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APPLICATION OF ENDOCRINOLOGY TO GYNECOLOGIC PROBLEMS*

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THERE are many clinicians whose interest, or lack of interest, in endocrinology is predicated upon their evaluation of the efficacy, or inefficacy, of organotherapy. This is a very narrow and unsound viewpoint.

The relief of human ailments is the natural goal of clinical medicine, but, so far as the gynecologic field is concerned, it may as well be admitted that the accomplishments of organotherapy have been very disappointing indeed. On the other hand, the advances in our knowledge of the physiology of reproduction have been brilliant, and much of this knowledge has been applicable in the interpretation of clinical problems in gynecology. The viewpoint of the gynecologist, so fortunate as to be interested in endocrinology, will inevitably be broader than that of his more mechanistic colleague, his insight into many problems deeper, and his daily work more full of satisfaction, interest, and zest. Such reasons as this should be incentive enough for the gynecologist to keep in touch with the scientific advances in his particular field of work, regardless of whether or not they are for the present applicable therapeutically.

When we stop to think that pretty much all we know of the physiology of menstruation pertains to its endocrinology, and that the physiology of reproduction has become one of the important physiologic problems, it is obvious that the gynecologist of today, if he is to practice his specialty intelligently, must of necessity be something of an endocrin-

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ologist. If the proper study of mankind is man, the proper study of gynecology is woman, in all her varied biologic aspects, rather than merely as a creature possessing pelvic organs of certain shape, size, and position. In many functional gynecologic disorders the implications of endocrinology are very obvious, in others less clearly evident, but each year adds new evidence that pathologic physiology as well as mere anatomic changes must be reckoned within the explanation of gynecologic disease. To illustrate by only the most recent example, we can no longer think of all ovarian tumors as purely parasitic nonfunctioning growths, for some of them, at least, we now know are capable of producing very profound endocrine effects upon the woman's body.

While the clinician has become quite dependent upon the laboratory worker for knowledge which may be applied in the diagnosis and treatment of disease, there is no need for him to play an entirely parasitic rôle in this regard. Many important endocrinologic advances have been made by clinicians, and many more can be made in the future, for the truth-seeking mind and the observant eye are not the monopoly of the experimental investigator, nor is there any scarcity of opportunity for research in the clinical field. It would be unfortunate if clinicians, through consciousness of many past indiscretions and excesses in the endocrine field, should develop such an inferiority complex as to inhibit their future usefulness as contributors to science.

Even the scientists are not beyond criticism, for much time, effort, and money have undoubtedly been wasted in studies which could not, by the farthest stretch of imagination, be considered to be of the slightest scientific, much less "practical" value. Many a problem which is perhaps illusory or self-evident has thus been profoundly settled by laborious and expensive experimentation, a brand of scientific investigation to which the Germans have applied the derisive designation of "Scheinwissenschaft." I need not reopen the old wounds inflicted by Lord Moynihan in his Toronto address in 1930,¹ when he so severely castigated the modern medical investigator for directing so little of his effort toward problems, the solution of which might in any way tend to lessen the ills of the human race. The quest of truth in itself is praiseworthy, but since it is always fragmentary, why cannot the medical investigator search especially for the fragments necessary to piece out our very imperfect knowledge of human disease?

This is not the place to review the advances which have been made in gynecologic endocrinology within recent years. I have tried to do this elsewhere,² with an expression of our indebtedness to our scientific co-workers in the experimental field. My own part in this symposium, I take it, should be to indicate how some of the raw material supplied to us by the laboratories may be applied in the interpretation and management of some of the more common gynecologic disorders.

With the possible exception of pain, the most important group of symptoms presented by gynecologic patients are menstrual aberrations of one form or another. To appreciate the significance of these abnormalities, a knowledge of the normal physiology of the cycle is fundamental. While the gynecologist himself may claim the credit for much of our knowledge concerning the menstrual histology of the ovarian and endometrial cycles, he is glad to acknowledge to the laboratory worker his indebtedness for most of what we know with reference to the physiologic forces behind these changes, although we have been kept busy trying to follow the frequent shifts of opinion on this subject.

For the present, it is accepted that both folliculin and progestin are important in the human reproductive cycle, whereas in the strictly sex cycles of the lower experimental animals the folliculin alone is the dominant hormone. In the human being, folliculin is present throughout the cycle, being formed first by the growing follicle and later by the corpus luteum, and possibly by other, as yet, unknown structures. Its function is to produce an increasing growth and hyperemia of the uterine mucosa and musculature. Progestin, on the other hand, makes its appearance in the cycle only after ovulation, and is concerned in the production of the secretory, preovulatory changes seen in the premenstrual epoch. No other source for progestin than the corpus luteum has as yet been discovered.

The evidence seems quite clear that the endocrine function of the ovary is physiologically subservient to that of the anterior hypophysis. There is still much to learn, however, as to this interlocking mechanism, although more and more it appears that the endocrine effects of the two glands are reciprocal, so that, as Moore³ and others have urged, the secretory activity of the ovary is an automatic and self-regulating one, through the reciprocal effects of excess or deficiency of the ovarian hormones upon the activity of the anterior hypophysis.

Another point which needs clarification is as to the relation of ovulation and menstruation. Certainly this relation is not an essential one, as has been abundantly shown by studies upon monkeys (Corner,⁴ Hartman,⁵ Allen⁶). But it is the human problem which needs elucidation on this point, and I think it is quite possible that anovulatory menstruation in women may be found to be much more common than is now believed. If this suspicion is borne out by future studies, we may have an explanation of many cases of sterility in which menstruation is perfectly normal in every way, and in which all the usual studies show no other ostensible cause for the sterility. It is unfortunate that thus far we have no method of determining, at least without microscopic examination of the endometrium, whether or not the individual woman is ovulating. The method of bimanual palpation, so successfully employed by Hartman in determining ovulation in the monkey, has so far been

of no value in this respect, and for rather obvious reasons, such as the frequent presence of atretic follicles not distinguishable by palpation from mature follicles.

As indicating the possibility of quite typical periodic bleeding, not differing from that of menstruation, in the entire absence of ovulation, I may mention the syndrome characterizing the so-called granulosa cell tumors of the ovary, now being reported with increasing frequency. When they occur in elderly women, as they most often do, it is common to observe an apparent reestablishment of the menstrual function, at least in the sense of a periodic uterine bleeding, and yet ova are not present in these tumors, nor does ovulation occur. The same thing is true in the case of granulosa cell tumor in very young children, of which several instances have been recorded.⁷ Here again menstruation is observed as a symptom, though without ovulation. In both instances the abnormal bleeding, whether precocious or postclimacteric, has been shown to be due to the production of folliculin by the granulosa cells of the tumor.

While both hormones undoubtedly play a part in the cycle of menstruation, the evidence points more and more to the fact that progestin plays no part in menstruation in the narrower sense of a periodic bleeding. The latter phenomenon appears to be entirely explainable by the fluctuations in the folliculin blood content. This view, now based on increasingly convincing evidence, is one which formerly seemed unacceptable to those of us, including myself, whose impressions were based on histologic rather than physiologic study. The chief paradox lay in the fact that the follicle reaches its maximum growth about two weeks before the onset of the bleeding.

With the discovery that, in the human at least, folliculin production is continued by the corpus luteum, this obstacle vanished. Again, the onset of bleeding shortly after the excision of the corpus luteum pointed to the latter as the natural inhibitor of the function, whereas now we know that excision of either the maturing follicle or the corpus luteum, both producing folliculin and the former only folliculin, is followed in due time by bleeding. The evidence therefore indicates that menstrual bleeding is a phenomenon produced by folliculin withdrawal. This is further supported by studies made upon castrated animals or amenorrheic women, in which bleeding is produced by folliculin injection, but only after the lapse of a number of days following the cessation of the injections.

In the same way, the intermenstrual bleeding seen in monkeys, as well as in some women, is apparently explainable by drops in the folliculin level occurring prior to the bleeding. If this concept of folliculin withdrawal is borne out by further work, and if it be extended to certain other types of bleeding, our whole former viewpoint of the mechanism

involved must be changed. In the very common gynecologic disorder spoken of as functional uterine bleeding, for example, it is not enough to speak of hyperfolliculinism as the underlying cause, as has been done in the past. For that matter, certain types of amenorrhea are likewise associated with folliculin excess, if correlated blood and urine studies are to be accepted as a guide. Some other factor, presumably causing an abrupt drop in the folliculin level, must be concerned in the profuse bleeding so often observed.

My own view is that the explanation of the bleeding is to be sought in the reciprocal interaction of the ovary and the anterior hypophyseal lobe. Moore,³ Hisaw and his coworkers,⁸ and others have shown that the secretory activity of the latter is inhibited by a sufficient dosage of gonadal hormone, and Moore's concept of sex hormone antagonism is based on this fact. It is logical, therefore, to assume that the excessive production of folliculin brings about such a pituitary inhibition, and that this in turn brings about a lowering of the folliculin production by the ovary. These drops in folliculin would explain the bleeding phases. Blood and urine hormone studies upon such cases during the bleeding and nonbleeding phases should be of great interest. What little evidence there is as yet available, however, indicates that the hypophyseo-gonadal relation is an automatic and self-regulating one, like that of a thermostat.

Theoretically, this form of bleeding should be amenable to treatment with folliculin, and this has indeed a measure of experimental support, but in clinical practice this has not proved to be the case, and such an artificial propping up of the folliculin level has its logical limits, not to speak of uncertainties in dosage. The best results thus far obtained in the organotherapy of this disorder have come from the administration of the so-called luteinizing principles of the urine of pregnant women,⁹ which appear to be the nearest clinical approach to supplying the progestin lacking in these cases, for the absence of corpora lutea is characteristic. There is, however, much uncertainty as to the mechanism involved in this form of treatment.

The recent observations of Kaufmann¹⁰ and Clauberg¹¹ have shown the possibility, in the human castrated patient, of producing hyperplasia of the endometrium by giving large dosages of folliculin, and then, in turn, of converting the hyperplastic endometrium into a pregravid one by means of progestin. The latter, if it becomes available for human use, may be looked to as offering the hope of successful treatment of this very frequent disorder, so often a most distressing one, especially in young patients where radiotherapy is so undesirable.

I have said nothing as yet as to the rôle of the anterior pituitary in the causation of functional hemorrhages, although there is general acceptance of the view that it is in the hypophysis that the underlying cause is to be sought. Leaving aside the discussion as to whether the sex

principle of the anterior lobe is single or dual, it is the follicle-ripening effect which seems to dominate in these cases, at the expense of the luteinizing factor. As yet, however, we have no means of correcting this dysfunction, or even of substitution therapy, unless we consider in this latter category the principles obtainable from the urine of pregnant women. Here again we collide with a controversy, for there is increasing evidence that these urinary substances are not identical with the pituitary sex hormones, although in most respects their physiologic properties are similar.

To pass to the other quantitative disorder of menstruation, amenorrhea, we encounter even more difficulty and confusion than in the consideration of menstrual excess. And yet, we have advanced far from the day when amenorrhea was explained only by a categorical list of such causes as anemia, obesity, and constitutional depravity, and even from the day when, with our new-found knowledge of hormones, ovarian hypofunction was added to the list. We know enough now to appreciate that the latter term may cover many endocrine sins, that the interplay of the ovarian secretions must be considered, and, even more, that the interdigitations of function between the ovary and the other ductless glands, especially the anterior pituitary lobe, cannot be overlooked.

By clinical methods alone in some cases, in others by such auxiliary methods as blood and urine hormone determinations, basal metabolism studies, or x-ray examinations, we can arrive at a fairly intelligent idea of the disorder concerned in the individual case, but not always. But, even if an intelligent endocrine diagnosis be made, rational organotherapy is not available in most cases. Those of thyroid origin are most favorable, both on the grounds of substitutional therapy and because the thyroid is believed to exert a stimulating effect upon many body functions. For the latter reason it is often employed even where a primary thyroid factor is not demonstrable.

For the immediate treatment of the menstrual deficiency, especially in cases in which we assume, usually on rather unscientific grounds, that a hypogonadism exists, some form of ovarian therapy is commonly resorted to, most often without success. The general appreciation of the futility of oral treatment with the older forms of tablets, capsules, or powders of ovarian or corpus luteum substances, or of ovarian residue, is chiefly due to the new light thrown on menstrual physiology, rather than to a mere crystallization of clinical experience and opinion.

With reference to the newer folliculin preparations for hypodermic use, for which such high hopes were originally held, disappointment has resulted, and here again our increased knowledge has enabled us to understand why this should be so. Theelin is capable of producing bleeding in at least a minority of amenorrheic women, but, from what has been said in preceding paragraphs, it is easy to understand that

it cannot reproduce the menstrual cyclic changes in either the uterus or the ovary. It is certainly not a stimulant of ovarian function, and, indeed, it is a depressant, as Hisaw and others have shown. To use theelin in amenorrhea is to push the pendulum of the run-down menstrual clock for a single idle, incomplete beat, when what we need is something to wind the clock.

The same may be said of theelol, the hydroxyl theelin derivative which has recently been introduced for clinical use and which is said to be active when given orally. With theelin the effective oral dose is many times, variously estimated as from ten to thirty, the dose required for hypodermic use.

Up to very recently, the question of the dosage of ovarian hormones necessary to bring about "menstrual" bleeding has been a matter of speculation, the point of departure being the dose necessary to bring about an estrous type of bleeding in animals. There was no direct evidence available from studies upon the human female. In the castrated monkey Hisaw, Meyer and Fevold,⁸ as well as Smith and Engle,¹² had been able to produce a pregravid endometrium by the use of folliculin followed by progestin, and the discontinuance of treatment was followed, in the observations of Smith and Engle, after six days, by what was apparently a typical menstrual bleeding. Clauberg's observation upon a young woman,¹¹ who had been castrated some years previously, is of interest, inasmuch as he was able to reproduce in her endometrium, by the use of the two ovarian hormones, a picture typical of the pregravid phase.

So far as I know, the only instance in the literature in which in the castrated human female a genuine menstrual cycle has been reproduced from beginning to end, including a typical menstrual bleeding, is in the extremely interesting case reported by Kaufmann.¹⁰ His patient had been castrated at the age of seventeen because of bilateral dermoids, and was of course amenorrheic. Five years later, by the injection of huge doses of folliculin, followed, with some overlapping, by correspondingly huge doses of the corpus luteum hormone, a typical menstrual flow was produced, with desquamation of uterine mucosa, which was recovered from the discharge. Microscopic examination of the cast-off tissue, as well as of further tissue removed with the curette, confirmed the genuinely menstrual character of the flow. The point to be stressed is that, in order to produce this cycle, 320,000 mouse units of the follicular substance (progynonbenzoate) and 90 rabbit units of the corpus luteum hormone were necessary. How fatuous therefore appear our efforts to treat amenorrhea by the injection of a few hundred units of theelin, either alone or in combination with some unsatisfactory substitute for the corpus luteum hormone, still so inaccessible to the clinician!

The huge dosages employed in the clinical experiments of Kaufmann and Clauberg bear out the deduction of Marrian and Parkes¹³ in a paper published in 1930. These investigators emphasized that the rat unit, as ordinarily employed, refers to the quantity of the hormone necessary to bring about the characteristic estrous changes in the vagina, but not in the uterus. To produce the latter, and to reproduce the sex behavior phenomena of estrus, 200 times the above dose is necessary, i.e., 200 units. If the human dosage is calculated on a weight basis, no less than 400,000 units would be needed to bring about the corresponding histologic transformation in the uterine mucosa. While weight is not necessarily a criterion of dosage, in this case it would appear that it is, for the calculated dose of Marrian and Parke is not very far out of line with the doses actually found necessary by Kaufmann and Clauberg.

Kaufmann properly criticizes the tendency to use as a gauge for dosage the amount of hormone eliminated in the urine, which should not be looked upon as necessarily indicating excretion because of an excessive amount in the blood stream. His contention that this hormone, before excretion, may have already played an important biologic rôle, appears to be rational. Furthermore, the recent recognition of several forms of folliculin (alpha, beta, theelol), each with a different grade of activity, helps to confuse the picture. But the chief moral to be drawn from this work would seem to be that, if we are to use substitutional ovarian therapy at all, we must work with far larger doses than has been the custom. Moreover, even with such large doses, there is still no evidence that we can expect a reinstitution of the function, for the therapy applies to the individual cycle alone, and would have to be repeated each month.

The dominating rôle of the anterior lobe over ovarian function would suggest that the key to wind the menstrual clock must be sought in the anterior hypophysis. Sometimes, however, the latter itself appears to be run down, and so where shall we seek? Moreover, pituitary therapy is still largely a blank, for the oral preparations now available are apparently worthless from both a clinical and experimental standpoint, and the hypodermic preparations of pituitary sex hormones, if such they really be, which are obtained from the urine of pregnant women appear to have little or no effect in the stimulation of ovarian function in the human being. All sorts of combinations have been suggested, such as the administration of growth hormone with these urinary principles (Evans, Meyer and Simpson),¹⁴ but no one is satisfied with results, and we are still floundering. It is to be hoped that some inspired scientist will soon see our signals of distress, and come to our rescue. In the meantime, it is consoling to know that amenorrhea is a symptom which

is rarely of any serious import to the patient, that in itself it causes no harm, and that proper explanation of this fact and reassurance of the patient is often the only treatment needed.

The last in the triad of most important menstrual disorders is dysmenorrhea, more particularly the so-called primary type. It is exceedingly common, and many factors may be concerned in its causation. There is considerable evidence that the immediate factor in the production of the pain may be a heightened irritability of the uterine musculature, and that this may be due to a relative excess of folliculin and a deficiency of progestin. The former appears to be the natural stimulant of uterine rhythmic contractility, the latter an inhibitor. This subject has been fully discussed in a very recent paper by Reynolds and myself,¹⁵ so that I shall not elaborate on it here.

With reference to the organotherapy of the severe symptoms sometimes noted at the menopause, either natural or artificial, little need be said, for I can add nothing that is new. The importance of general regulatory measures and of simple sedatives is accepted by all, but there is much difference of opinion as to the possibilities of organotherapy. The most popular form of the latter, for the present at least, appears to be the administration of theelin, most often hypodermically. Whether or not the favorable results often reported by the patient are to be explained on a purely psychic basis I confess I do not know. Since theelin is undoubtedly deficient in some phases of the menopause, there is at least a semblance of scientific support for its use at this epoch.

The clinician is often hard put to it in his efforts to relieve the very distressing symptoms seen in a small proportion of menopausal patients, and, if the simpler general measures do not avail, I for one shall continue this form of ovarian therapy, at least until further studies give us a more efficient plan of management. In this connection, it seems both curious and unfortunate that so little effort has been made to discover the mechanism involved in the production of the hot flushes and the other vasomotor phenomena so characteristic of the menopause, in spite of the fact that the problem presents very obvious difficulties.

Perhaps the outstanding contribution of endocrinology to clinical practice has been in the development of the first satisfactory biologic test for pregnancy, for the Aschheim-Zondek test, as well as its various modifications, may be looked upon as important by-products of the present-day feverish interest in reproductive endocrinology. As already stated, there is still much discussion as to whether the urinary substances upon which the test is dependent are of pituitary or placental origin, but this question has no bearing on the reliability and value of the test in the diagnosis of normal pregnancy, or its application in the management of such abnormal types as tubal pregnancy, hydatidiform mole, or chorionepithelioma. One advance leads to another, for already it is

certain that the remarkable multiple lutein cyst formations in the ovaries of patients suffering with either hydatidiform mole or chorion-epithelioma are not true tumors, but that they represent merely an abnormal ovarian response to the abnormal endocrine stimulus emanating from the anterior hypophysis in such cases.

Numerous other examples of the applications of endocrinology in the field of gynecology might be adduced. I have already mentioned that these extend even to the field of ovarian tumors, and I have discussed this general subject in two forthcoming papers. The skeptics of former days are the converts of today, and some of our wisest pathologists appear to be impressed with the potentialities of endocrine studies in relation to tumors, not excluding cancer itself. It will be seen from what has been said that in the field of gynecology, organotherapy has thus far yielded very unsatisfying results, but the therapeutic reward for all the splendid scientific work which has been done is sure to come sooner or later. Why wait for this day to develop an interest in endocrinology, which even in its still undeveloped state can freshen our viewpoint concerning so many clinical problems which had been giving every indication of growing stale?

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26 EAST PRESTON STREET

THE EFFECT OF CHANGES IN THE AMOUNT OF PROTEIN UPON PREGNANCY AND LACTATION*

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THE practice of modern obstetrics calls for many things which were unknown a generation ago. Among these is the question of diet. To date this must still be considered controversial in many of its aspects. No one can deny that whatever the baby requires and receives in pregnancy must be furnished by the mother and ultimately through what she herself eats. Under ordinary circumstances and where a varied and reasonably well-chosen diet is taken there is such an abundant supply of all the necessary elements of a diet that the process of feeding the unborn infant can almost be considered to be automatic and foolproof. With, however, the devitalization which is so frequently found in many of our modern foods and with the unbalanced diets which so many women take, particularly as regards an excess of carbohydrates, it is also evident that suboptimal diets can and are being taken. No one knows exactly what harm may result from the taking of such partially inadequate dietaries. The experimental approach to such a problem may give us some clue as to what to expect with human beings. It was with that purpose in mind that the experiments to be reported this evening were undertaken.

There is moreover another reason why it is important to know what harm may result either to mother or fetus from the limiting of food. This reason is to be found in the desirability of limiting the gain in weight which certain pregnant women exhibit where nothing is done to control the amounts of food eaten. It seems to be pretty generally believed by obstetricians that if the mother is not allowed to gain too much, excessively large babies can be avoided.¹ There are also some who believe that the complications of pregnancy which are known to be more frequent in patients who are overweight can at least to a certain extent be reduced in frequency by keeping the gain low. For all these reasons then more accurate information is greatly to be desired and may have extremely important practical results.

Of all the questions as to the amounts of various elements which go to make up a normal diet that as to protein has been most in dispute. Standards for the amounts and sources of protein even today are doubtful, hence it is natural that there should be an ever greater divergence of opinion as regards these points in pregnancy. Apart from the lime of the skeleton the body of the growing fetus is made up chiefly of

*NOTE.—The experimental work upon which this paper is based was carried out in the Research Laboratory of the Department of Obstetrics, Harvard Medical School. It was aided by grants from the DeLamar Fund.

various compounds of protein. It would seem logical therefore that the requirement for a nonpregnant woman would have to be increased during pregnancy. On the other hand, there are certain writers who stress the danger of too much protein in the diet, claiming that such an excess may be a direct cause of nephritis (see Newburgh²). Pregnancy puts an extra load on the kidneys. The toxemias of pregnancy are characterized in part by albuminuria and other evidences of renal insufficiency. In this dilemma what is the obstetrician to do? If the expectant mother takes too little protein in her diet the baby may be partially starved or her own tissues may be called on to supply the deficiency. If she takes too much there is at least the threatened danger that she may be damaging her already overworked kidneys.

No experimental research on animals, and particularly on the lower mammals, can be expected to duplicate conditions which are found with human beings. It is therefore very necessary to be cautious in drawing any direct inferences from what happens in one species as to what may be expected in another. Broad trends are more indicative than are slight deviations from the normal. With this caution in mind much of a suggestive nature can, however, be learned from animal experimentation.

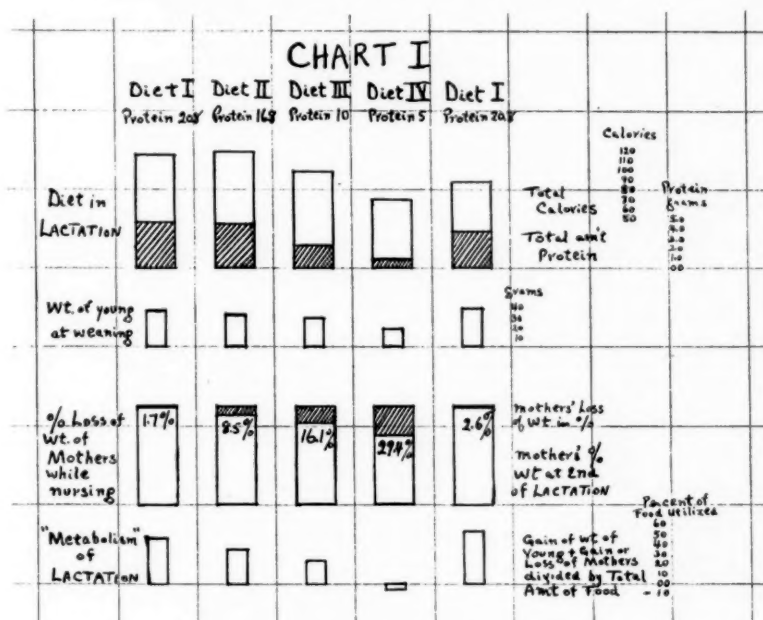
For the purpose of testing what effect different amounts of protein may have upon pregnancy and lactation, the white rat was chosen as the most suitable animal; first, because much of the preliminary work had already been done by other investigators, and, second, because of the ease with which this animal lends itself to investigations of this sort.

Protein has long been recognized as an important element in reproduction. In fact, the general impression has been that the amount of protein not only affects reproduction, but may be a limiting factor as it is in the growth of young.

In 1922, Evans and Bishop³ published some work on this point, but as the diets used contained only fat and protein, and their observations on the effects produced by changes in the percentage of protein upon reproduction were limited to the occurrence of estrus, no deductions can be drawn. In 1924, Simmonds⁴ reported a large series of experiments showing the effect of changes in the percentage of protein upon reproduction and lactation. Diets ranging from 67 down through 57, 40, 35, 31, 21 to 9 per cent protein were used. In general lactation was not adversely affected by percentages above 21 (the control) though many of the mothers eventually suffered kidney changes. Nine per cent was chosen for many of the diets, since it was found that the proteins had to be of good quality for lactation to succeed. If the proteins were largely from animal sources, lactation was found to be fairly normal even at this figure, but many failures occurred and the weights of the young at weaning were never as good. Furthermore, the mothers lost more weight. The main criticism of this work is, applicable to all percentage feeding experiments, namely, that the actual amounts ingested were not known.

There have been practically no other investigations reported on this subject until the past year when J. R. Slonaker⁵ came out with four articles in the *American*

Journal of Physiology on "The Effect of Different Per Cents of Protein in the Diet." Among other things the effect of the changes in protein upon reproduction was studied. The five diets used were so constituted that they had equal energy producing qualities combined with 10, 14, 18, 22, and 26 per cent protein respectively. The work was well done and the results are instructive. There is only one criticism and that is as to the sources of the vitamins. The diet did not contain cod liver oil and very little butter (1 per cent); yeast was 0.4 per cent; wheat germ 0.6 per cent. The authors soon found that the diet was deficient in vitamin B, and this was corrected by adding fresh brewers yeast, but vitamins A, D and E, while sufficient for reproduction, would seem to have been suboptimal. All the diets were made up from Diet I (protein 10 per cent) by adding meat scrap. This while increasing the protein could not help decreasing the percentage of vitamins, and the higher the percentage of protein, the lower must have been the percentage of



these important elements. One cannot help wondering whether some of the ill effects noted with animals on these higher percentages may not have been due to slight deficiencies in these vitamins. In every instance the reproductive performance of rats on Diet II (protein 14 per cent) was superior to that of rats on other percentages. Fertility was higher, and there was less sterility, the animals continued reproducing longer, the average number of litters was greater, and the average number of young was higher; more young were brought to weaning. One strange fact was noted, namely, that the fertility of the males was greatly decreased over that of the females. Even on Diet II, where female fertility was 100 per cent, that of the males was only 87 per cent. Could this also be the result of a diet low in vitamin content? Deficiency in vitamin B is known to affect males, even causing testicular atrophy in extreme cases. This work of Slonaker, though important and carefully worked out, was also carried out by percentage feeding methods. No idea of actual protein intake can be obtained from the experiments as reported.

The present series of experiments was designed to be a quantitative investigation into the effect of changes in the amount of protein ingested upon reproduction in-

cluding fertility, pregnancy, and lactation. Four diets were used which may be designated according to the percentage of protein they contained; I 20 per cent, II 16 per cent, III 10 per cent and IV 5 per cent. The protein* used was commercial casein which is known to be adequate in all the amino acids necessary for growth. The other constituents of the diet were identical except for the fact that the percentage of starch was increased to compensate for the lessened percentage of protein. The control diet (Diet I, protein 20 per cent +) was made up as follows: casein 20 per cent; salt mixture IV (Osbourne and Mendel⁶) 4 per cent; starch (corn starch) 51 per cent; wheat germ 5 per cent; powdered yeast extract (Harris) 2 per cent; cod liver oil (Patch) 2 per cent; butter 16 per cent. Later a small amount of fresh lettuce was fed daily, also for a while 10 per cent wheat germ was used with a corresponding increase in the total protein to 21 per cent.†

TABLE I

	DIET I	DIET II	DIET III	DIET IV
Casein	20	16	9	4
Salt mixture	4	4	4	4
Starch	51	55	57	62
Wheat germ	5	5	10	10
Yeast	2	2	2	2
Cod liver oil	2	2	2	2
Butter	16	16	16	16
	100	100	100	100
Protein	20.8%	16.8%	10%	5%

The method of procedure was substantially as follows: At least 10 adult females were kept on Diet I. Later 10 more were added, making 20 in all which were used entirely as controls. Ten were put on Diet II and after a sufficient period of observation these rats were shifted to Diet III, and later to Diet IV. Finally these same 10 rats were themselves placed on Diet I. Other parts of the experiment regarding energy metabolism, vitamin E, etc., will be reported in subsequent papers and at that time more data will be given about the other methods of procedure with other rats.

These females were kept in individual cages and a daily vaginal smear was taken. At the same time the food put in was weighed, and the food taken out uneaten from the previous day. In this way daily food consumption was accurately known, and the actual amount of any given constituent could easily be computed. The rats themselves were weighed each day. When the female was found to be in Stage 1, 2, or early 3, a fertile male (on stock diet) was introduced. If spermatozoa were found, next day he was removed, if not, he was left until Stage 5 smears were found, and then removed. This was repeated until

*The total protein also includes that contained in the wheat germ and lettuce.

†These changes were instituted because of the fact that the original diet was low in vitamin E and consequently a large number of absorptions took place. Lard was used as the first fat in the proportion of 20 per cent. This neutralized the E as reported by Evans⁷. At the time we were not aware of this effect of a rancid fat and tried increasing the wheat germ and adding lettuce as well as changing the lard to butter.

pregnancy took place. The occurrence of pregnancy was checked by continued Stage 5 smears, placenta sign, gain in weight of mother and palpation. When young were born, they were individually weighed on the day of birth, but thereafter only the total litter weight was recorded each day. At first the whole litter was allowed to nurse, but with the reduced diets this was found to be too much of a strain on the mother, with subsequent failure of the young to develop until the time of weaning. Therefore after the second month the litters were all cut down to six at birth.

Following Simmonds' work, and also using a diet similar to that in calcium experiments by me,⁸ it was determined to use 20 per cent protein in the control diet (I). This was before Slonaker reported optimum performance on 14 per cent though, as noted above, there is some doubt as to whether the adverse effects reported by him are actually the result of the increase in protein or of the decrease in vitamin content. Simmonds' diets very high in protein permitted normal reproduction and lactation.

The actual record was as follows:

On Diet I (protein 20.8 per cent with lard as source of fat).—Nine out of 9 rats promptly became pregnant, but there were 4 absorptions (due to the fact that the lard destroyed the vitamin E). Five litters of young were born with 44 young. Only one mother was able to nurse her young, and she raised 9 out of 11 with an average weight of 27.7 gm. at twenty-one days. Because of the fact that this diet was deficient the results may be eliminated from this part of the discussion. Diet I unless specifically qualified then will be understood to have the analysis recorded in Table I of Protein 20.8 per cent and butter 16 per cent.

Corrected Diet I (protein 20.8 per cent, butter 16 per cent).—Ten out of 10 mothers became pregnant giving birth to 102 young. Only 5 mothers were able to nurse their young, raising 33 out of 47 until time of weaning. The average weight of the young was 36.6 at twenty-one days.

This did not seem to be a very good result on what was supposed to be a normal diet. An attempt was therefore made to improve Diet I still further by adding a small amount of lettuce each day (about 10 gm.). With this change these same rats again became pregnant giving birth to 109 young. This time 8 of the 10 were able to nurse their young, raising 58 out of 73 until time of weaning. The average weight of the young at weaning was 36.2. While this record of performance was not perfect, part of the trouble seemed to be due to the fact that, because of some individual peculiarity, two mothers were never able to raise a litter no matter how many pregnancies occurred or what the diet was. On the same diet another group of 10 mothers all became pregnant, giving birth to 83 young. The litters were cut down to six (whenever the number at birth exceeded that figure) and 52 young out of a possible 57 were raised until time of weaning. The average weight of the young at weaning was 42.2 gm. each.

On Diet II (protein 16.8 per cent with butter).—Nine out of 9 became pregnant, giving birth to 86 young. Only 6 mothers were able to nurse their young, raising 46 out of 47 with an average weight at weaning of 31.5 gm. each, an excellent performance.

On Diet III (protein 10 per cent with butter).—Ten out of 10 became pregnant, giving birth to 74 young. Again only 6 mothers were able to nurse, and raised 37 out of 45 to weaning with an average weight for the young at weaning of 30.1 gm. each. The performance here also was surprisingly good.

On Diet IV (protein 5 per cent with butter and lettuce).—Nine out of 9 became pregnant, giving birth to 70 young. On this diet only 5 mothers nursed, raising 22 out of 28 to an average weight of 19.8 in twenty-one days.

When put back on *Diet I* (protein 20.8 per cent with butter and lettuce) 7 out of 7 became pregnant, giving birth to 49 young. Six mothers were able to nurse, raising 29 out of 30 in sixteen and six-tenths days to an average weight of 39.8 gm. each! Such a performance speaks for itself.

Turning now to the amounts of food eaten and the calculated analysis we obtain some very interesting figures. These are shown in Tables II and III. On all diets the amount of food eaten was about the same during pregnancy and contained roughly the same number of calories. The amount of protein, however, decreased progressively from a total daily amount of 2.90 gm. to 2.52, 1.44 and 0.83. On these amounts the

TABLE II. SUMMARY OF DATA FOR PREGNANCY

	NUMBER OF MOTHERS	DAILY AM'T OF FOOD	DAILY AM'T OF PROTEIN	DAILY NO. OF CALORIES	MOTHERS' GAIN OR LOSS	LITTER SIZE	AV. WT. OF YOUNG
Diet I, protein 20.8	10	14.5	2.90	68	+21.3	10.9	5.25
Diet II, protein 16.8	9	14.8	2.52	69	+28.3	9.5	5.25
Diet III, protein 10	10	14.4	1.44	66	+29.5	7.4	5.57
Diet IV, protein 5	9	14.9	0.83	69	+22.9	7.7	4.98
Diet I, protein 20.8	7	14.1	2.82	66	+27.5	7.0	5.10

TABLE III. SUMMARY OF DATA FOR LACTATION

	NUMBER OF MOTHERS	% ABLE TO NURSE	DAILY AM'T OF FOOD	DAILY AM'T OF PROTEIN	DAILY NO. OF CALORIES	MOTHERS' GAIN OR LOSS	NO. NURSED PER MOTHER	% OF YOUNG RAISED	AV. WT. AT WEANING
Diet I	8	80	24.2	4.84	114	- 4.0	7.6	93	36.2
Diet II	6	66	25.4	4.32	119	-19.3	9.0	85	31.5
Diet III	6	60	21.6	2.16	99	-40.5	7.0	88	30.1
Diet IV	5	55	15.4	0.86	72	-74.0	5.6	78	19.8
Diet I	6	87	19.0	3.80	89	+ 6.3	5.0	96	39.8

litter size decreased also from approximately 11 through 9.5 to an average of $7.5 \pm$. Even returning these animals to a normal protein did not bring the litter size back to the original figures. The average weight of the individual young at birth has been found to vary with the litter size. The reduction in the amount of protein in the mothers' diet did not change this until the minimum protein intake of 0.83 was reached;

on this diet the young were not quite up to standard, but the difference was trifling. Furthermore, the mothers' usual gain during pregnancy was practically the same on all diets. To summarize: reduction in the amount of protein had little apparent effect upon conception and pregnancy beyond a reduction in fertility, and a slight effect upon the weight of the young when the reduction was extreme.

The effect upon lactation was much more striking and in this respect duplicates the result of the similar work previously done on calcium.⁸ Though the reduced amount of protein had shown so little apparent effect on pregnancy something had been taking place as is well shown by the decreasing percentage of mothers able to nurse at all. This fell from 80 per cent progressively to 55 per cent on Diet IV and rose to normal, or even above, when these animals were replaced on Diet I. The amount of food eaten (in grams) was roughly three times the number of young nursed, except that on Diet IV it was decidedly less than this and, as if to compensate, was a great deal more when the animals were put back on Diet I. The calories followed the amounts eaten. The total daily protein dropped from 4.84 through 4.32 and 2.16 to 0.86. The mothers lost a progressively greater and greater amount of weight until returned to Diet I. Altogether there was much better performance than could have been anticipated. On Diet I both before and afterward 95 per cent of the young which began to nurse were raised to weaning. On Diets II and III the average was still high, 85 per cent for 9 and 88 per cent for 7 respectively. On Diet IV in spite of a reduction to 5.6 nurslings each only 78 per cent were raised to weaning. Even more striking was the effect upon the weight at weaning (twenty-one days). This fell from the normal of 35 or better to 30 for Diets II and III and 20 for Diet IV.

In studying these results it is evident that in spite of very drastic changes in the protein the fetus or the nursling suffers relatively little, and that it is the maternal organism which, by drawing on its reserves, is able to make up for the lack in the diet. Compare the loss for the mother during the three weeks of nursing with the average weight of the nurslings on Diets I, II, and III. On Diet II the loss is five times as great, and on Diet III ten times as great, while the young weigh only about 16 per cent less! On Diet IV the amount of protein ingested is so slight that even a loss eighteen times the normal is unable to protect the young, and they weigh from 44 to 50 per cent under what they should.

Some of these changes have been shown graphically in Chart I. This needs no comment beyond that already given, except that the last row of graphs has been given to show in a rough way the relationship between the amount of food eaten and the results obtained in maternal and filial loss or gain. To denote these changes the term metabolism has been used in its most general sense, which relates more to material

transformations than to any energy changes which took place. These latter were not measured and no estimate of them can be given. It seemed, however, worth while making some simple calculations in regard to the former changes. No account was taken of water, but daily gain of mothers plus fetuses or nurslings was figured as the numerator of a fraction of which the daily amount of food eaten was the denominator. The fraction expressed in percentage form is called the metabolism. Two facts stand out, first, that the metabolism (percentage of food utilized in growth) is much higher in lactation than in pregnancy and, second, that the metabolism of lactation is much more adversely affected by a lessened protein intake than is that of pregnancy.

SUMMARY

On a diet containing 20 per cent protein, where the daily consumption was 2.9 gm. of protein, fertility was optimum. Progressive reductions in the daily protein intake to a minimum of 0.83 gm. reduced fertility. These changes did not, however, materially affect pregnancy. This failure to affect pregnancy in the rat should not, however, be interpreted as meaning that pregnancy might not be affected in a larger mammal where the young are born at a later stage of development.

The effect upon lactation was very definite. As the daily amount of protein ingested fell from 4.84 to a minimum of 0.86 gm., a smaller percentage of young was raised to weaning, the average weight of the young at weaning was less, and the loss of weight suffered by the mothers during lactation was greater. Finally, with the reduction in the amount of protein eaten the metabolism during lactation fell below zero.

Such being the results of the experimental work, what conclusions, if any, are we justified in drawing as to what is likely to happen in human pregnancy and lactation under similar conditions? Bearing in mind the caution already stated that we can never draw close parallels between any two species, it would, nevertheless, seem justifiable to state that there is probably an optimum protein requirement during pregnancy and lactation for man just as there is for the rat.

It is interesting to note in passing that if one takes the amount of protein fed in Diet I during pregnancy in its ratio to the number of calories ingested and applies this to human beings, 125 gm. of protein would be needed with a total of 3,000 calories. The ratio for Diet II comes out roughly 100 gm. for 3,000 calories. This approximates very closely with what many investigators have held to be the optimum for man. Such an amount of protein, that is between 100 and 125 gm. would seem to many too high, but in our experiments just quoted a smaller amount invariably caused injury either to mother or fetus, and there is a strong presumption that similar reductions would have sim-

ilar effects in human pregnancy. During lactation it has been found by certain observers, and with certain patients, that as many as 4,500 calories may be ingested. The amount of protein for this number of calories, using the same ratio found in the rat experiments, would be about 187 gm. on Diet I and 150 gm. on Diet II. These amounts are large but not larger than those found by Macy⁹ for the three women whom she studied intensively. As a rule it is the mother who suffers. Up to a certain point the baby acts as a parasite and gets what it needs from the mother's tissues provided she is not taking sufficient of the element involved in her diet. This was conclusively proved for calcium in the work already referred to where it could be shown by x-rays of the mother's bones, by the condition of her teeth and by the result of chemical analysis after the animal was killed. In every case where there was a long-continued deficiency in the diet the mother suffered. Both with calcium and with protein where the deficiency was great the fetus suffered as well. This was shown by slower rate of growth with the total weight at weaning much less than where the diet was normal. For mothers on Diet IV, protein 5 per cent, this parasitic action was most marked. The mothers lost a great deal of weight (29.4 per cent) during lactation, but the young were still able to gain though slowly. When the young at the time of weaning, however, were put on the same food eaten by the mothers, they were unable to gain while under observation for a period of three weeks. Their previous gain therefore must have resulted from protein which the mothers had lost in order to supply milk. These same young when put on a diet containing an adequate amount of protein were able to gain in a perfectly normal manner.

CONCLUSION

In this paper certain dietary experiments with the white rat have been reported which show that there is an optimum amount of protein for pregnancy and lactation. If the amount of protein is below the optimum, first, the mother suffers by losing protein from her tissues, and, second, if the deficiency is extreme the young suffer so that the rate of growth and development is greatly retarded. It is suggested that there is a similar optimum requirement of protein, probably somewhere between 100 and 125 gm. per day, for human pregnancy and lactation. This requirement is undoubtedly greater for lactation than for pregnancy, but with the greater development undergone by the human fetus before birth, there is a corresponding greater requirement for protein. It is also suggested that perhaps one of the reasons why certain women do not stand pregnancy and lactation well may be connected with the serious drain which a diet deficient in protein may impose upon them at those times.

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THE EFFECTS OF PREGNANCY ON THE ORGAN WEIGHTS OF THE ALBINO RAT

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INTRODUCTION

IN REVIEWING the available literature on the effects of pregnancy on the organ weights of animals and man, it is surprising to find that the amount of work that has been done on this subject is very minimal. While numerous histologic studies have been made of organs from pregnant animals, there are very few reported observations on gross organ weights. One finds innumerable statements to the effect that this or that organ hypertrophies or atrophies during pregnancy, but few authors cite the actual weights.

This investigation was undertaken in an attempt to establish a preliminary set of figures to which further work may increase our knowledge of the effect of pregnancy on organ weights.

I wish to express my sincere thanks to Drs. J. C. Litzenberg, C. M. Jackson, and J. A. Urner, for their help and encouragement.

MATERIALS AND METHODS

The animals used in this study consisted of 66 female albino rats (*Mus Norvegicus*) of the Wistar strain, bred from normal adult males and females, maintained upon a routine stock diet, and reared in the animal colony of the Department of Anatomy at the University of Minnesota.

The 44 animals to be investigated as pregnant ones were impregnated at 175 gm. body weight without considering their ages, because of the difficulty in securing a sufficient number of rats of both the same age and weight in the time allotted for the experiment. Animals of the same weight were taken as far as possible, the age being somewhat more variable.

The 22 animals to be used as controls were killed as soon as they had reached the weight of 183 gm., that is, about 8 gm. heavier than the rats to be impregnated. This was done because it has been shown by Freudenberger (1932) that, in the Minnesota Colony, the rat at around 175 gm. will normally gain about 15 or 16 gm. in the next three weeks. In other words, the controls were killed when they had gained half of the weight that the pregnant animals would have gained in the three weeks if they had not been pregnant. This was done so as to set a better standard for comparison and to eliminate a source of error in the consideration of the mean weights of the animals.

In discussing the figures obtained three comparisons are made. The control animals are compared with the animals in the first half and with those in the latter half of their pregnancies. The animals of the first half are also compared with those in the latter half of their pregnancies.

In computing the probable error of a mean, the following formula was employed:

$$\text{P.E.} = 0.6745 \frac{\delta x}{\sqrt{N}}$$

The formula used in arriving at the probable error of the difference between two means is:

$$\sqrt{\text{P.E. } \bar{x}_1^2 + \text{P.E. } \bar{x}_2^2}$$

If it is found that the difference between two means divided by the probable error of the difference is more than three, this difference is considered as a significant one. This ratio will be called the "significance ratio." If this significance ratio is between two and three, the significance of the difference is considered questionable.

DISCUSSION

Age of Rats, Body Weight, Body Length, Tail Length and Weight of Head

The reader is referred to Table I which shows the mean weights and probable errors of the various data, in the controls, first half and second half of pregnancy.

Age.—When we compare the ages of the control rats with those of the pregnant ones, we find that the significance ratio for the first eleven days is 5.47, and for the last eleven days is 2.62. For the comparison between the first and the last eleven days, the significance ratio is 2.09. We may assume then, that in the comparisons made in this experiment, our most important results may be deduced from the comparison made between the controls and the last eleven days of pregnancy and that between the first eleven days and the last eleven days of pregnancy, because in these cases both the ages of the rats and their weights, on which the experiment is based, are directly comparable.

Body Weight.—A large number of investigators have studied the effect of pregnancy on the body weight, particularly in the case of the human female. On the other hand, there are but very few recorded observations on the effect of pregnancy on the body weight or body length in experimental animals.

Gassner (1862), Baumm (1887), Heil (1896), Kruger (1907), Zangemeister (1916), Lorenzen (1921), and others agree that the human pregnant organism increases in weight during gestation aside from the increase in weight due to the uterus and its contents. Watson (1905) in a study of female white rats, and Hartwell (1927) in a study of large series of pregnant white rats, conclude that the maternal organism increases in weight during pregnancy aside from the increase in weight due to the uterus and its contents. Herring (1920) states, on the other hand, that "in the healthy albino rat the occurrence of pregnancy has little effect upon the body weight or body length, excluding the increase of weight due to the uterus and its contents." Herring's observations were made on only 9 pairs of rats, half of which were used as controls and half of which were impregnated.

TABLE I. MEANS, AND PROBABLE ERRORS, FOR THE VARIOUS DATA IN THE CONTROLS, FIRST HALF AND SECOND HALF OF PREGNANCY

ORGANS	22 CONTROLS	22		22	
		FIRST HALF OF PREGNANCY		SECOND HALF OF PREGNANCY	
Age (in days)	107.10 ± 3.87	142.43	± 5.17	125.86	± 6.02
Body weight	185.64 ± 0.19	186.00	± 1.21	213.18	± 2.39
Corrected body weight	185.64 ± 0.19	185.29	± 1.18	197.13	± 1.31
Body length (cm.)	19.99 ± 0.044	20.00	± 0.015	20.33	± 0.015
Tail length (cm.)	19.18 ± 0.081	19.60	± 0.020	19.76	± 0.12
Head	16.91 ± 0.070	17.14	± 0.11	17.63	± 0.12
Submaxillary glands	0.373 ± 0.0057	0.352	± 0.0045	0.379	± 0.0076
Brain	1.86 ± 0.010	1.84	± 0.0098	1.84	± 0.014
Hypophysis	0.0105 ± 0.0002	0.0109	± 0.0001	0.0096	± 0.0002
Eyeballs	0.258 ± 0.0010	0.277	± 0.0028	0.269	± 0.0030
Thyroid	0.0315 ± 0.0009	0.0238	± 0.0006	0.0239	± 0.0008
Thymus	0.357 ± 0.0098	0.273	± 0.013	0.249	± 0.011
Heart	0.688 ± 0.0081	0.683	± 0.0078	0.704	± 0.0062
Lungs	1.058 ± 0.0074	1.126	± 0.029	1.089	± 0.030
Liver	7.52 ± 0.15	7.89	± 0.16	9.65	± 0.40
Spleen	0.397 ± 0.0057	0.456	± 0.0096	0.422	± 0.0095
Stomach and intestines with contents	14.047 ± 0.082	16.26	± 0.32	17.74	± 0.53
Stomach, empty	0.81 ± 0.012	0.87	± 0.051	0.89	± 0.015
Intestines, empty	4.21 ± 0.078	5.97	± 0.25	5.38	± 0.19
Suprarenals	0.0439 ± 0.0007	0.0417	± 0.0007	0.0448	± 0.0006
Kidneys	1.57 ± 0.018	1.59	± 0.021	1.63	± 0.022
Ovaries	0.0562 ± 0.0015	0.0506	± 0.0009	0.0681	± 0.0019
Uterus	0.391 ± 0.0029	0.586	± 0.015	2.043	± 0.096
Left femur	0.560 ± 0.0051	0.564	± 0.0015	0.591	± 0.0013
Left humerus	0.250 ± 0.0022	0.245	± 0.0021	0.261	± 0.0024
Skeleton and musculature	99.64 ± 0.84	99.71	± 0.784	103.05	± 1.022
Left femur and musculature	8.08 ± 0.127	8.87	± 0.14	8.79	± 0.093
Left humerus and musculature	1.80 ± 0.048	1.92	± 0.037	1.99	± 0.042

From my investigation it may be seen that in comparing the control series of rats with the pregnant rats of the first eleven days in regard to body weight and corrected body weight, there is no significant increase in body weight in the first eleven days of pregnancy, the significance ratios being 0.27 in both cases. On the other hand, comparing

the controls with the last eleven days of pregnancy, we find a very definite increase in body weight and corrected body weight in the case of the pregnant rats; the significance ratios are 11.19 and 7.99 respectively. We may assume from this, that the body weight of the pregnant animals, aside from the increase due to the uterus and its contents, is very definitely greater than in the case of the control animals. Further, when we compare these same measurements of the first half with those of the last half of pregnancy, we find that the body weights of the animals are significantly greater in the last half of pregnancy over those of the first half of pregnancy. The significance ratios are 10.14 for the body weight and 6.71 for the corrected body weight. Upon comparing the average weight of the animals before impregnation with their average weight in the two halves of pregnancy, we find that the weight has significantly increased as a result of the pregnancy. This increase is aside from that due to the weight of the uterus and its contents. The significance ratio for the comparison between the weight of the animals before impregnation and their weight in the first half of pregnancy is 8.31. The ratio for the comparison between the rats before impregnation and their average weight in the latter half of pregnancy is 16.33.

Body Length.—The body length of the test animals shows no significant difference from that of the control animals in the first half of pregnancy. In the last half of pregnancy, comparing the test animals with the controls, we find a significance ratio of 5.23, showing a significant increase in body length in the case of the pregnant animals. There are two possible explanations for this, first, that the congestion of the tissues and softening of the joints in the case of the pregnant organism may be sufficient to allow of an easily increased stretching of the body; second, the increase in body length may be due simply to skeletal growth associated with the increased body weight. Upon comparing the animals of the first half with those of the last half of pregnancy, we still find the significance ratio up to 4.80.

Tail Length.—I have been able to find no reference in the literature as to the effect of pregnancy on the tail length of the maternal organism. Comparing my control animals with my test animals from the first half of pregnancy, I find a significance ratio of 3.98 which rises to 4.01 in the last half of pregnancy, and decreases to 1.20 upon comparing the first half with the last half of pregnancy. I am forced to the conclusion that the tail length of the pregnant rats is significantly greater than that of the control rats in both the first and last halves of pregnancy, and that there is no difference in tail length upon comparing the animals of the first half with those of the last half of pregnancy.

Head.—Considering now the weight of the head and comparing the controls with the test animals of the first eleven days, we find a significance ratio of 1.68, of no statistical importance. When we compare the test animals of the last eleven days of pregnancy with the controls, however, we find a significance ratio of 5.24, and upon comparing the first eleven days of pregnancy with the last eleven days of pregnancy, we still find a significance ratio of 3.02. We may assume that in the two latter comparisons the head weighs significantly more in the case of the animals of the last eleven days. I can explain this only by saying that the head increases in weight coincidentally with the increase in weight of the rest of the maternal organism.

ORGAN WEIGHTS

Organs Showing No Significant Changes: Brain, Heart, Kidneys, Lungs, Skeleton and Musculature

Watson (1905) in a study of the effect of pregnancy on the weight of the central nervous system of albino rats, stated that the mated rats in his experiment had both absolutely and proportionately a heavier nervous system. There has apparently been no experimental work done in which the effect of pregnancy on the weight of the heart has been accurately determined. Practically all of the work reported is of a clinical nature. Liesenfeld, Dahmen and Junkersdorf (1927) state that "the relative weight of the heart increases in the first half and decreases in the last half of pregnancy." Schmidt, Bickenbach and Jonen (1927) state that the relative weights of the heart, spleen, and kidneys at the end of pregnancy, in a series of dogs, lie at the lower level of normal. Herring (1920) states that the kidneys of rats are little affected by pregnancy, but that the liver is greatly enlarged. MacKay (1928), from a study of the effects of pregnancy and lactation on the renal weights of albino rats, came to the conclusion that the kidney weights of two groups of albino rats killed when two hundred and twenty days of age, were not affected by pregnancy which had terminated for one group at approximately eight days previously and for the other about forty-five days before. I can find nothing in the literature to which I may compare the data that I have obtained on the effect of pregnancy on the lungs. Wiltshire (1869) stated, "The cardiac and nearly the whole of the voluntary muscles are increased by childbearing and this process may truly be said, therefore, to influence the muscular development of women." He cites no organ weights. I have found no skeletal weights recorded for pregnant animals.

From the data that I have obtained on the series of rats investigated, I must conclude that pregnancy has no significant effect on the weights of the brain, heart, kidneys, lungs, or skeleton and musculature.

ORGANS SHOWING SIGNIFICANT CHANGES

Eyeballs.—Upon comparing the weights of the eyeballs of my control rats with the weights of those of the pregnant animals of the first half and of the last half of pregnancy, I find significant ratios of 4.6 and 2.94 respectively. When I compare the weights between the first and last halves of pregnancy, I find a significant ratio of 1.94. Why the eyeballs of the rats from the first half of pregnancy should be significantly heavier than those of the control animals is a question I am not able to answer. Nothing was found recorded in the literature to which I may compare my data.

Hypophysis.—Comparing now the hypophyses of the rats from the first half of pregnancy with those of the controls, we calculate a significance ratio of 1.4; upon comparing the glands of the rats of the last half of pregnancy with those of the controls, however, we find a difference between the means of -0.0009 ± 0.0003 and a significance ratio of 3.33. The significance ratio for the comparison of the glands of the first and last half of pregnancy is 1.75. From a survey of the literature, there seems to be no doubt that the hypophysis of the human female enlarges during pregnancy. Compté (1898) first described this hypertrophy in the human female. Compté's conclusions have been confirmed by a number of workers, notably Erdheim and Stumme (1909), Launois and Mulon (1904), Bartlett (1913), Goetsch (1917), and a number of others. Herring (1920) in an investigation of a series of pregnant white rats states in contrast to the above, that in the rat "there is a notable diminution in the weight of the pituitary gland as a result of pregnancy." Ac-

cording to Schenk (1925), the animals that show changes similar to man are the cat, rat, and guinea pig. Schenk, after an investigation of a series of pregnant white rats, states further that, "there is no doubt, that the increase in size and weight of the hypophysis is not difficult to confirm." Although the various investigators agree upon the change in the hypophysis in the human pregnant female, there is a definite contradiction of opinion in the case of the rat. My work tends to confirm that of Herring quoted above. I find that the hypophysis of the rat in the latter half of pregnancy is definitely smaller than the gland from the control animals, the significance ratio being 3.33 as noted above; however, there is no significant difference between the weights of the glands of the first half of pregnancy and those of the controls. From a study of rats including the present series, Stein (1931, 1932) likewise found no evidence of an increased weight in the hypophysis during pregnancy.

Stomach and Intestines.—I have been able to find nothing in the literature to which I might compare my data on the stomach and intestines. Upon comparing the stomach and intestines (with contents) of the control animals with those of the pregnant animals of the first eleven days, I find a significance ratio of 5.3; upon comparing the same organs of the control animals with those of the pregnant animals of the last half of pregnancy, I find a significance ratio of 6.23. In both cases, the weights of the stomach and intestines with contents of the pregnant animals are significantly greater than those of the control animals. It may be of interest to note here two articles by John and Schick (1923) and Wang (1925) in relation to body weight and the food intake of pregnant rats. These authors agree that during gestation there is no increase in the food intake of rats, so that an explanation of the increased weights of the organs considered above cannot be on the basis of increased food materials in the gastrointestinal tract. There is no significant difference in weights between the organs of the first and last halves of pregnancy, the significance ratio of 2.39 being of only questionable importance.

It may be of interest at this point to consider separately the empty stomach and the empty intestines. Upon comparing the empty stomachs of the animals of the first half of gestation with those of the controls, we find a significance ratio of 2.7, the difference here being of only questionable significance. Upon comparing the stomachs from the animals in the last half of pregnancy with those of the controls, we note a significance ratio of 4.23. We must assume then that the stomach increases in weight in the latter half of pregnancy for some reason as yet undetermined. There is, however, no significant difference between the organ weights of the first and latter halves of pregnancy.

The weight of the empty intestines from the animals of the first half of gestation compared with those of the controls shows a significance ratio of 6.7, whereas in the latter half of pregnancy the ratio is only 1.79. We must assume here that the empty intestines increase in weight in the first half of pregnancy and that there is no difference in the last half of pregnancy. Nothing was found in the literature to which I may compare my findings.

Liver.—One of my most interesting observations has been that in regard to the liver. Upon comparing the liver weights of the rats from the first half of pregnancy with the weights of the livers from the controls, I find a significance ratio of 1.6; apparently the liver does not change significantly in weight in the first half of pregnancy. In the comparison of the latter half of pregnancy with the controls, I find, however, a significance ratio of 15.60, one of the largest ratios obtained, being exceeded only by that of the uterus. The comparison of the liver weights from the first half with those from the last half of pregnancy shows a significance ratio of 4.03. The mean difference between the liver weights of the second half of pregnancy and the controls is 2.13 gm. with a probable error of ± 0.14 . My findings

agree with those of Herring cited previously and with those of MacKay (1928) who stated that the liver of the pregnant rat increased 19.5 per cent in relation to body surface.

Left Femur and Musculature.—Now considering separately the left femur and attached musculature. Upon comparing the weights in the first half of pregnancy with the controls, we find a significance ratio of 4.2. Comparing the weights in the second half of gestation with the controls, we find a ratio of 4.01, and upon comparing the first half of gestation with the latter half, we calculate a ratio of 0.52. The left humerus and musculature of the animals from the first half of pregnancy compared with the controls shows a ratio of 1.9. The left humerus and musculature of the latter half of pregnancy compared with the controls shows a ratio of 1.17, and the comparison between the first and last halves of pregnancy yields a ratio of 1.20. If we consider now the left femur and the left humerus devoid of any tissue, we find that upon comparing the weights in the latter half of pregnancy with the controls, the significance ratios are 4.67 and 3.39 respectively. The first half of pregnancy shows no significant change in weight over that of the controls. Further, comparing the femur and humerus of the latter half of pregnancy with the first half of pregnancy, we find significance ratios of 4.27 and 4.49 respectively. From a consideration of the above, I do not feel that it would be safe to draw conclusions in regard to the effect of pregnancy on the skeleton and musculature. Why the two bones should show an increase in weight in the second half of pregnancy and why this increase does not show up in the comparison of the entire skeleton and musculature, I cannot explain. It may be that the skeleton being so much smaller than the musculature, the results obtained with regard to it may be swamped. I feel that it would be safest to draw a general conclusion from a consideration of the significance ratios for the skeleton and musculature only, that is, that pregnancy has no effect on the weight of this structure.

Ovaries.—Stotsenburg (1923) has made the only observation that I have been able to find in regard to the effect of pregnancy on the ovaries. He states that "the ovaries of the albino rat in pregnancy are generally heavier than those in unmated females, except after the fourteenth day of lactation, and when the female is deprived of her litter, the regular loss in weight of the ovaries is curtailed and the ovaries tend to remain heavy up to thirty days after casting the young." In my experiment, upon comparing the mean of the weights of the ovaries of the controls with the mean weights of the ovaries from the animals in the first half of pregnancy, I find that the ovaries of the control animals are heavier than those of the pregnant animals. The difference is -0.0056 gm. and the probable error is ± 0.0018 . The significance ratio is 3.2. We must conclude that the ovaries of the pregnant animals of the first half of pregnancy are significantly smaller in weight than the ovaries of the controls. Upon comparing the controls with the animals of the latter half of pregnancy, we find that the ovaries of the pregnant animals are heavier, the difference being 0.0119 ± 0.0024 gm. and the significance ratio being 4.90. When we compare the first half with the latter half of gestation, we find a significance ratio of 8.37. The ovaries then, show a significant decrease in weight in the first half of pregnancy and a significant increase in weight in the latter half of pregnancy over the weight of the controls. There is further, a significant increase in the weight of the ovaries from the animals in the latter half of pregnancy over those of the first half of pregnancy.

Spleen.—Upon examining the mean weights of the spleen, we find that in the first half of pregnancy the spleen shows a significant increase in weight over that of the control animals; the significance ratio is 5.2. In the latter half of pregnancy the change in weight is questionable, the ratio being 2.3. Upon comparing

the first half with the latter half of gestation, the ratio is 2.53, again of questionable value. My findings do not agree with those of Barcroft and Stevens (1928) who have shown by exteriorizing the spleens of dogs that during pregnancy there is a definite shrinking of the organ and a marked decrease in its volume.

Suprarenals.—Upon comparing the suprarenals of the three groups of animals, we find very little difference in weights. The glands of the pregnant rats of the first eleven days are questionably smaller in weight than the glands of the controls, the difference between the mean weights being -0.0022 gm. and the significance ratio being 2.3. The suprarenals of the animals from the last eleven days of pregnancy show no significant change over the glands from the controls, the ratio being 0.95. Upon comparing the weights of the glands from the first half of gestation with the weights of those of the last half of gestation, the ratio is 1.09, showing no significant change in the two halves of pregnancy. There are numerous reports in the literature on the effect of pregnancy on the suprarenals, but the results are contradictory. Guieysse (1901) who investigated the changes in the adrenals of pregnant guinea pigs found that they showed a marked hypertrophy. Kolde (1913), found no changes in the adrenals of pregnant dogs. Herring (1920) stated that the suprarenals of rats are slightly hypertrophied during pregnancy. Donaldson (1924) stated that no increase in weight of the adrenals occurred during pregnancy. My calculations lead me to the conclusion that in the pregnant albino rat, the pregnancy does not cause a hypertrophy of the suprarenal glands that may be determined by weighing.

Submaxillary Glands.—The submaxillary glands of the rats from the first eleven days of pregnancy compared with the glands of the controls show a difference in mean weight of -0.020 gm., and significance ratio of 2.7; the glands of the pregnant animals being questionably smaller in weight than the glands of the controls. The comparison between the last eleven days and the controls shows no difference, the significance ratio being 0.79. Upon comparing the weights in the first half with those in the latter half of pregnancy, we find a barely significant ratio of 3.04. Why this should be so, I have not been able to determine. Nothing was found in the literature with which I might compare my results.

Thymus.—The consensus of opinion in regard to the effect of pregnancy on the weight of the thymus is consistent, in that all of the men who have worked on this subject agree that pregnancy increases the rapidity of the normal atrophy of the thymus. Henderson (1904) was the first to observe that when heifers have been pregnant for several months, the normal atrophy of the thymus is greatly accelerated. Fulei (1913) reports the same effect in rabbits, and Herring (1920) states, "The thymus in pregnant rats is much diminished in size." Hammar (1926) cites evidence which permits us to suppose that in human beings, the thymic atrophy is accelerated in pregnancy. Schaffer in 1908 described the rapid involution of the thymus during pregnancy in the mole. Utterström made the same observation in the rabbit. Jolly and Lieure (1930) show, as a result of their experiments that the glands of pregnant guinea pigs are much more involuted than those of nonpregnant animals of the same age. My findings agree unequivocally with those of the above investigators. Upon comparing the mean weight of the thymus of the controls with the mean weight of the glands from the test animals of the first half of pregnancy, we find that the glands from the pregnant animals are definitely smaller in size, the difference in weight being -0.084 gm. with a probable error of ± 0.016 , and a significance ratio of 5.1. Upon comparing the controls with the animals of the latter half of pregnancy, we find again that the mean weight of the glands from the pregnant animals is less than that of the controls, the difference in weight being -0.108 gm. with a probable error of ± 0.015 , and a significance ratio of 7.36. There is no significant difference found upon comparing the weights of the glands from the two halves of pregnancy.

Thyroid.—Considering now the thyroid gland, I find that upon comparing the mean weight of the glands of the pregnant animals from the first half of pregnancy with the mean weight of the glands of the controls, the glands of the pregnant animals are again smaller than those of the controls, the difference being -0.0077 ± 0.0011 gm., and the significance ratio being 7.1. The same holds true in the latter half of pregnancy. The difference in weight is -0.0076 ± 0.0011 gm., and the significance ratio is 6.63. There is no significant difference between the gland weights in the two halves of gestation. In contrast, it is apparently agreed that the thyroid gland of the human female enlarges during pregnancy. Lawson Tait (1875), Caro (1905), Marine (1917), Knaus (1923), Marine, Cipra, and Hunt (1924), Daly and Strouse (1925), and numerous other investigators offer this opinion. The only investigations in animals that I have been able to find were one by Lowe (1930), who found that the thyroid glands of pregnant cats were on the whole more actively secreting than those of normal males, and one by Herring (1920) who investigated rats, and whose findings agree with mine.

Uterus.—There are a number of articles in the literature on the weight of the uterus in pregnancy. The most interesting of the group is the reference by Mondino who, as early as 1493, noted the enlargement of the uterus as a result of pregnancy. My findings are interesting not in that they show a significant increase in weight of the uterus, but rather that they give a good idea as to the actual increase in the weight of the uterus of the albino rat as a result of pregnancy. Comparing the mean weights of these organs from the controls with the mean weights of the organs from the animals of the first half of pregnancy, I find that the average increase in weight is 0.195 gm., and the significance ratio is 4.1. In the latter half of pregnancy, the mean increase in weight of the uterus over that of the controls is 1.65 gm. with a significance ratio of 17.04. Comparing the two halves of pregnancy, the mean increase in the weight of the uterus in the latter half over the weight in the first half is 1.46 gm. and the significance ratio is 13.57.

VARIABILITY (TABLE II)

It may be of interest at this point to mention briefly the effect of pregnancy on the variability of the measurements taken in this study. I shall begin with a group of organs and measurements of relatively low variability; in this group it may further be noted that with but few exceptions, pregnancy has no effect on the variability of the measurements. Included in this group are the eyeballs, kidneys, heart, left femur, left humerus, skeleton and musculature, brain, tail length, head, body weight, and body length. The body length has the lowest coefficient of variation and is not affected by pregnancy. The body weight comes next under the control group, but it may be noted that the variability of the body weight increases progressively as the pregnancy advances. The head shows a slightly increased coefficient of variation in the pregnant animals over that of the controls. The tail length also shows a slightly increased degree of variability in the latter half of pregnancy only. The variability in the remainder of the group is practically unaffected by pregnancy and remains low.

In the next group of organs to be considered the degree of variability is moderate. This group includes the liver, hypophysis, stomach and intestines with contents, empty intestines, suprarenals, empty stomach,

TABLE II. COEFFICIENTS OF VARIATION

ORGANS	CONTROL	FIRST 11 DAYS PREGNANT	LAST 11 DAYS PREGNANT
Age	24.5	24.6	33.2
Thymus	19.1	33.8	30.2
Thyroid	19.0	16.8	23.0
Ovaries	18.5	12.0	19.5
Left humerus and musculature	17.3	13.2	14.3
Lungs	15.3	17.8	18.6
Liver	14.1	9.1	29.0
Hypophysis	13.3	9.1	13.5
Stomach and intestines with contents	12.8	13.5	20.8
Intestines, empty	12.8	27.6	24.6
Suprarenals	11.1	11.0	9.3
Stomach, empty	10.9	13.1	11.8
Submaxillary glands	10.6	8.9	13.9
Left femur and musculature	10.1	10.8	7.1
Spleen	9.9	14.7	15.7
Uterus	8.6	55.0	32.9
Eyeballs	8.2	7.2	6.8
Kidneys	8.2	9.3	9.6
Heart	8.2	7.9	6.1
Left femur	6.2	5.7	5.1
Left humerus	5.8	5.8	6.5
Skeleton and musculature	5.4	5.4	6.7
Brain	3.9	3.7	5.3
Tail length	2.8	2.3	4.2
Head	2.7	4.6	4.6
Body weight	2.2	4.5	7.8
Body length	1.5	1.7	1.6

submaxillary glands, left femur and musculature, spleen, and uterus. Starting at the bottom of the group again, we note that pregnancy greatly increases the variability of the uterus, the coefficient of variation being highest during the first half of gestation. The spleen shows a slight increase in variability as a result of pregnancy. The left femur and musculature show a slightly decreased degree of variability in the latter half of pregnancy only. The empty intestines and liver show an increased variability as a result of pregnancy while the submaxillary glands, empty stomach, suprarenals, and hypophysis show practically no change in variability at all.

In the last group to be considered, we have those organs and measurements which show the highest degrees of variability. Included in this group are the age, thymus, thyroid, ovaries, left humerus and musculature, and lungs. The lungs, left humerus and musculature, and ovaries show very little change in variability as a result of pregnancy. The thymus and thyroid show an increasing degree of variability as the pregnancy progresses.

SUMMARY AND CONCLUSIONS

A series of 44 pregnant and 22 control nonpregnant albino rats were investigated to determine the effect of pregnancy on the organ weights of the body.

The body weights of the rats were taken as nearly comparable as possible. The controls were autopsied at 183 gm.; the test animals were impregnated at 175 gm., their final weights averaging 186 gm. in those killed in the first half of pregnancy, and 213 gm. in the second half of pregnancy.

In the comparison between the control rats and the rats of the first half of pregnancy, the following differences were found: The tail length, eyeballs, spleen, stomach and intestines with contents, empty intestines, uterus, and left femur and musculature, all show significant increases in weight in the first half of pregnancy. An uncertain increase in weight is also noted in the case of the stomach. The body weight, corrected body weight, body length, head, brain, hypophysis, heart, lungs, liver, kidneys, left femur, left humerus, skeleton and musculature, and left humerus and musculature, show no significant changes in weight as a result of pregnancy. The thyroid, thymus, and ovaries show significant decreases in weight. In the case of the submaxillary glands and suprarenals, the decrease in weight in the first half of pregnancy is questionable.

In the comparison of the controls with the animals of the latter half of pregnancy, we note differences as follows: The body weight, corrected body weight, body length, tail length, head, liver, stomach and intestines with contents, empty stomach, ovaries, uterus, left femur, left humerus, and left femur and musculature, all show significant increases in weight as a result of pregnancy. The increases in weight in the case of the eyeballs, spleen, and skeleton and musculature are statistically questionable. The submaxillary glands, brain, heart, lungs, empty intestines, suprarenals, kidneys, and left humerus and musculature, show no significant weight changes. The hypophysis, thyroid, and thymus show significant decreases in weight as a result of pregnancy.

Upon comparing the first and last halves of pregnancy, we note the following differences: The body weight, corrected body weight, body length, head, submaxillary glands, liver, ovaries, uterus, left femur, and left humerus, show significant increases in weight in the latter half of pregnancy. The heart, stomach and intestines with contents, and skeleton and musculature, show questionable increases in weight in the last half of pregnancy. The tail length, brain, hypophysis, eyeballs, thyroid, thymus, lungs, empty stomach, empty intestines, suprarenals, kidneys, left femur and musculature, and left humerus and musculature, show no changes. The spleen shows a questionable decrease in weight in the latter half of pregnancy.

In the comparison between the controls with the animals of the first half of pregnancy, there is a significant difference in age between the two groups; in the comparison between the controls with the animals of the latter half of pregnancy, and in the comparison of the

animals of the first half with those of the last half of pregnancy, the differences in age are of only questionable significance.

From a study of the graphs of those organs showing the most marked changes are drawn the following conclusions: The body weight and the weight of the liver increase gradually from the beginning of pregnancy, but the increase seems to be most rapid after the first half of pregnancy. The weights of the thyroid and thymus are apparently affected at the very onset of gestation and they continue to be lower than normal throughout pregnancy. The weight of the spleen seems to increase rapidly in the first half and then return to normal in the latter half of pregnancy. The ovarian weights remain normal during the first half but show a striking increase in the latter half of pregnancy. The weight of the uterus increases gradually from the beginning to the end of gestation.

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DIFFUSIBLE SERUM CALCIUM IN PREGNANCY

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A NUMBER of investigators have established the fact that maternal serum calcium is lowered during the terminal stages of pregnancy, but rises at parturition and during the postpartum stage.^{1, 2, 3} There are only two available reports about the diffusible portion of the maternal serum calcium.

Watchorn and McCance⁴ estimated the total and the diffusible calcium in the sera of twelve normal pregnant women in the thirty-second to the thirty-eighth week, and found the average total calcium level to be 9 mg. per 100 c.c., with 64 per cent diffusible. The normal nonpregnant value for the method they used (Greenberg and Gunther⁵) is about 50 per cent. Aburel and Ornstein-Cernantianu⁶ determined the diffusible calcium in six pregnant women using a similar low pressure method of ultrafiltration, and found the total calcium to average 9.1 mg. per 100 c.c. at delivery, with 61 per cent diffusible. These authors also analyzed the cord blood in a similar manner and showed that the fetal calcium level (11.2 gm.) is distinctly higher than the maternal, but that the proportion of the diffusible calcium is definitely lower (55 per cent) in the fetal specimens. It has been previously well established that the total calcium level in the fetal blood is 1 to 2 mg. higher than in the maternal.^{7, 8, 9}

DIFFUSIBLE SERUM CALCIUM IN NORMAL PREGNANCY

Ten white women, in the eighth lunar month of pregnancy, were selected from the Out-patient Department. These women were reg-

TABLE I. TOTAL CALCIUM, DIFFUSIBLE CALCIUM AND PHOSPHORUS IN MATERNAL
SERUM IN NORMAL PREGNANCY

PERIOD	TOTAL CALCIUM		DIFFUSIBLE CALCIUM		PHOSPHORUS	
	MIN.	MAX.	MIN.	MAX.	MIN.	MAX.
	mg.		mg.	per cent	mg.	
Eighth month, antepartum	9.4	10.6	6.7	71	4.0	5.0
	(10.1)*		(7.8)	(77)	(4.4)	
Ninth month, antepartum	9.1	11.3	6.5	63	2.9	5.0
	(9.9)		(7.6)	(77)	(4.2)	
Tenth month, antepartum	8.7	11.1	7.0	74	4.2	5.0
	(9.8)		(7.8)	(80)	(4.7)	
During labor	8.6	10.8	6.4	64	4.1	7.1
	(9.6)		(8.2)	(85)	(4.9)	
Twenty-four hours postpartum	9.1	11.1	4.8	43	3.9	6.3
	(10.0)		(7.0)	(70)	(5.1)	
Forty-eight hours postpartum	9.4	11.1	4.9	52	4.3	6.3
	(10.2)		(6.7)	(66)	(5.6)	

*Average values are in parentheses. All concentrations expressed in milligrams per 100 c.c. of serum.

TABLE II. CALCIUM AND PHOSPHORUS IN MATERNAL AND CORD SERUM IN ABNORMAL CONDITIONS OF PREGNANCY

CASE	TOTAL Ca	DIFFUSIBLE Ca		PHOS.	SAMPLE* TAKEN	REMARKS
	mg.	mg.	per cent	mg.		
1	10.2	7.7	75	5.0	Eighth month	At delivery, mother afebrile. 48 hours of labor with delivery of stillborn. One month postmature (?)
	10.4	8.2	79	4.2	Ninth month	
	7.1	4.3	60	10.0	Delivery	
	9.7	6.1	63	3.9	24 hr. postpartum	
2	10.5	7.6	72	4.0	Eighth month	In labor for 20 hours, otherwise normal.
	9.2	7.4	80	5.0	Ninth month	
	10.0	4.2	42	5.0	Delivery	
	11.1	4.8	43	5.9	24 hr. postpartum	
3	9.9	8.9	90	4.0	Eighth month	In labor 12 hours, with disproportionately long second stage. Nine-and-one-half-pound baby.
	12.1	8.0	66	5.9	Delivery	
	10.3	7.4	72	5.0	24 hr. postpartum	
	10.0	6.0	60	5.0	48 hr. postpartum	
4	9.8	7.6	77	4.4	Delivery	Postpartum eclampsia, one convulsion. Blood pressure 190/120, with 4+ albuminuria. Baby toxic.
	9.4	5.4	57	7.3	Cord	
	9.8	6.3	64	3.3	36 hr. postpartum	
5	9.2	7.6	83	4.3	3 hr. postpartum	Primipara, twenty-four years old. Slight rise in blood pressure just prior to delivery. Labor five hours, no albuminuria. Placenta normal.
	9.1	8.8	97	5.9	Baby, 3 hr. old	
	9.7	7.0	72	4.0	5 days postpartum, mother	
	10.9	5.7	54	4.0	2 mo. postpartum, mother	
6	12.2	7.6	62	6.7	Delivery	Preeclampsia, death of fetus in utero. Blood pressure 210/150. Stillborn macerated fetus.
	10.7	7.9	74	4.7	3 days postpartum	
	10.6	6.8	64	3.0	14 days postpartum	
7	12.0	12.0	100	16.7	Delivery	Fulminating eclampsia, died in convulsions. Blood pressure 210/110.
8	9.4	9.1	97	8.0	Delivery	Nephritis of pregnancy with convulsions. Child stillborn.
	10.8	9.3	86	10.7	Cord	
9	9.4	7.5	80	4.8	2 days antepartum	Nephritic toxemia, ablation placenta. Death of fetus in utero.
	9.5	7.3	77	5.3	Delivery	
	8.9	7.1	80	6.3	24 hr. postpartum	
	8.7	8.2	94	5.9	72 hr. postpartum	
10	8.8	5.3	60	4.3	Eighth month	Herpes gestationis. Child normal, and postpartum period normal.
	10.0	6.5	65	4.8	Delivery	
	11.5	6.0	52	6.2	Cord	

*The sample is maternal serum unless marked cord or baby. All concentrations expressed in milligrams per 100 c.c. of serum.

ularly examined semimonthly, and blood samples for analysis were taken once a month. They were also delivered in the hospital and cared for during a three-day puerperium. Since these women were charity patients, it is fair to assume that their diet was of rather low calcium and phosphorus content, but no direct observations were made. Total and diffusible calcium determinations were made by the method of Nicholas,¹⁰ the actual calcium analyses being made according to the method of Clark and Collip.¹¹ Inorganic phosphorus determinations were made by the method of Fiske and Subbarow.¹²

Table I summarizes the data obtained in these ten cases, with the following exceptions: Three of the patients presented normal ante- and postpartum courses, but their labors were decidedly abnormal. Therefore, the data on the delivery samples of these three women are not included in Table I, but are presented separately in Table II.

Examining the data in Table I, one notes that the total calcium drops rather uniformly during the late months of pregnancy, reaching a low point at delivery, and then returns to normal within the next two days. The diffusible calcium fraction at the eighth month is considerably higher than the normal nonpregnant values for the method used,¹⁰ and increases to its peak value at delivery with a rapid falling off in concentration, during the first two days of the puerperium to a normal nonpregnant value of about 6.5 mg. The inorganic phosphorus content increases steadily during the antepartum period, and continues to increase during the first forty-eight hours after delivery. Serum albumin and globulin determinations by the method of Greenberg¹³ were also made at all stages, with the results showing very little fluctuation and conforming to similar values given by Plass and Matthew.¹⁴

These results need very little comment. The most significant fact is that the maternal diffusible calcium is definitely increased during pregnancy, regardless of the method of determining this fraction. Cantarow,¹ using the calcium content of cerebrospinal fluid as an index of the diffusible calcium concentration, notes an increase; and Watchorn and McCance⁴ and Aburel and Ornstein-Cernantianu,⁶ using methods of mechanical ultrafiltration at low pressures (150-600 mm. Hg) arrive at the same conclusions. Our determinations were made by ultrafiltering serum through cellophane at 150 pounds pressure, a method which seems to yield higher values for *normal* diffusible calcium than do other low pressure methods. The relatively greater values for diffusible calcium in pregnancy are therefore to be expected. That is, maternal serum in the late months of pregnancy carries between 77 and 85 per cent of the total calcium in a diffusible form as compared to the normal value, for the method used, of 64 per cent. The mechanism underlying this change in the concentration and partition of serum calcium in pregnancy cannot from these data be determined. Cantarow¹⁵ suggests that this condition is produced either directly, due to the drain by the fetus on the maternal organism, or indirectly by some disturbance in the parathyroid function under the influence of the pregnancy.

DIFFUSIBLE SERUM CALCIUM IN ABNORMAL LABOR AND PREGNANCY

The three patients, mentioned above, who had abnormal labors, are presented in Table II. Case 1 was normal until the time she entered the hospital in labor. The total calcium soon after the onset of labor showed almost a tetanic level (7.1 mg.) with a very low diffusible calcium value (4.3 mg.). After forty-eight hours' labor she was delivered

of a stillborn child. The postpartum period was uneventful. The time of death of the fetus in utero in relation to the taking of the blood sample was not noted. It is impossible from this one case to decide just what effect the death of the fetus in utero might have had on the maternal calcium level. One might say that with the death of the fetus the need for calcium is removed and the maternal organism immediately tends to readjust itself to a normal blood calcium level, first showing a drop in the total and diffusible calcium levels with a tendency to return to normal values as is shown in the twenty-four-hour postpartum sample.

Case 2 was similar in some respects to Case 1. The patient had a normal antepartum course, but was in labor twenty hours. The delivery sample showed a high total calcium, but a decidedly low diffusible calcium content, which remained low during the first twenty-four hours of the puerperium. The child, however, was normal and the mother showed no other abnormalities. The patient in Case 3 was in labor for twelve hours with a disproportionately long second stage, delivering a nine-and-one-half-pound child. At delivery, there was a relatively high total calcium with a normal diffusible calcium level. The blood calcium levels in this case, however, are not as divergent from the normal delivery values as are the results in the other two cases. It is possible that the time of obtaining the blood samples with reference to the stage and duration of labor should be more closely controlled, since Cantarow¹ has shown that there is considerable difference between the total calcium levels in the first stage of labor (9.6 mg.) and the second (10.3 mg.).

Cases 4 to 10 inclusive were patients who presented abnormal pregnancy pictures, but whose serum, in general, had not been analyzed during the antepartum period. The serum calcium in Case 4 was normal, although the patient had one postpartum convulsion. The baby was definitely toxic, but soon returned to normal without any therapy. Case 5 was similar to Case 4, although no definite diagnosis of toxemia in the mother was rendered. The baby, however, was very definitely toxic, and had to be given emergency treatment for tetany. The blood calcium studies in these two cases are more interesting from the standpoint of the child. Both babies showed a low neonatal total calcium level, that is, a calcium content *below* that of the maternal serum (see Table III). The baby of Case 4, however, showed a relatively lower proportion of diffusible calcium (which is normally found); whereas the baby of Case 5 showed a very high proportion of diffusible calcium, and the baby was decidedly tetanic. A full discussion of this case has been published,¹⁶ and more cases showing this phenomenon have been studied recently. It is, of course, impossible to draw any conclusions from two cases, but it seems as though a cord calcium content *below* that of the mother is indicative of some toxic symptoms in the child, whether or not the mother shows any toxemia.

Cases 6 and 7 were diagnosed as typical eclampsia. The total calcium level was distinctly high (over 12 mg.), a variation previously reported by Cantarow,¹ and by Stander, Duncan and Sisson.¹⁷ However, Anderson¹⁸ in a more recent paper reports very low calcium values (below 9 mg.) in 82 per cent of his forty-four cases of eclampsia. The amount and proportion of the diffusible calcium in the two cases is widely divergent. In Case 6 the diffusible calcium was rather low at delivery, whereas in Case 7 the diffusible calcium portion represented all of the total calcium. Cases 8 and 9 were diagnosed as shown in the table, with both babies stillborn. Neither mother presented a picture similar to Cases 1, 6, and 7, who also delivered

stillborns. The cord blood of the stillborn in Case 8 showed a normal relationship to the maternal calcium level, as compared to the data of Table III.

Case 10 was a classical example of herpes gestationis. The maternal serum calcium picture at the eighth month and at delivery were not normal, there being a low total calcium level at the eighth month and a relatively high value at delivery. The diffusible calcium level was distinctly low on both samples. Calcium therapy was tried but proved of no value. The clinical aspects of this case are to be reported by one of us (R. A. J.) later.

It is impossible to draw any definite conclusions relative to the level or proportion of diffusible calcium in maternal serum from these few cases of abnormal pregnancy or labor. The duration and difficulty of labor, the death of the fetus in utero and the toxemias of pregnancy certainly seem to influence the calcium content of both maternal and cord serum. What benefit may be expected from calcium therapy in eclampsia, in view of the serum calcium findings, is still problematical. Minot and Cutler¹⁹ who believe that the production of guanidine bases is one of the factors in the causation of eclamptic symptoms, have reported beneficial results by the use of calcium salts intravenously and intramuscularly. The present authors²⁰ have shown that tyramine is present

TABLE III. THE RELATIONSHIP OF MATERNAL TO CORD SERUM CALCIUM AND PHOSPHORUS IN NORMAL PREGNANCY*

TOTAL CALCIUM MIN. MAX.	DIFFUSIBLE CALCIUM		PHOSPHORUS		
	MIN. MAX.	MIN. MAX.	MIN. MAX.	MIN. MAX.	
mg. 9.6 - 12.4 (10.2)	mg. 6.3 - 10.0 (8.0)	per cent 61 - 99 (78)	mg. 2.7 - 6.2 (4.8)		Maternal serum
11.0 - 13.6 (12.2)	6.8 - 9.0 (7.9)	50 - 82 (65)	4.4 - 13.3 (7.2)		Cord serum
8.8	8.7	99	6.2		Maternal serum
11.2	9.0	80	5.5		Cord serum, first twin
11.0	9.0	82	5.7		Cord serum, second twin

*Average values are in parentheses. All concentrations expressed in milligrams per 100 c.c. of serum.

in eclamptic serum, and still others believe that histamine is the toxic principle involved. The nature of the relationship of serum calcium or of calcium therapy to any of these possible toxic amines, that are undoubtedly present in eclampsia, cannot at present be determined. However, there seems to be one possible connecting link, namely, the parathyroids. There is some evidence which indicates that the parathyroids control the detoxication of guanidine derivatives,²¹ and moreover, these glands are known to control serum calcium level. Therefore, if pregnancy does disturb the normal function of the parathyroids there is quite likely to be some intimate relationship, in eclampsia particularly, between the serum calcium level and the toxic action of guanidine, tyramine, or histamine. The function of the parathyroids in pregnancy, therefore, needs further investigation.

THE RELATIONSHIP OF MATERNAL TO CORD SERUM CALCIUM

Table III gives the data obtained in 8 normal deliveries, including one set of twins. The majority of the maternal samples were obtained in the delivery room just previous to the cutting of the cord and the taking of the fetal sample. It will be noted that the average total calcium level of the maternal serum at delivery is somewhat higher (10.2 mg.) than the average value given in Table I. The "during labor" values as given in Table I were obtained from the parturients early in the first stage of labor, i.e., as soon as they entered the hospital. These data confirm the findings of Cantarow¹ that the total calcium is higher in the second stage of labor than in the first.

In all 8 cases, the total calcium content of the cord exceeded that of the maternal serum by 1 to 3 mg. per 100 c.c., whereas the absolute level of the diffusible calcium was about the same in both specimens, although the percentage of diffusible calcium in the cord serum was distinctly and invariably lower than that of the maternal serum. These data confirm the findings of Aburel and Ornstein-Cernantinau⁶ for normal pregnancy. The data on the mother and the twins (which are included in the general averages) are presented in detail at the end of Table III. The data show the uniform distribution of calcium and phosphorus between the two twins, and the mother.

CONCLUSIONS

1. Maternal serum calcium decreases during the late months of pregnancy, reaching a low concentration at delivery, then increases during the early puerperium.
2. Maternal diffusible calcium, both relatively and absolutely, increases during the late months of pregnancy, reaching a high level at delivery, and then decreases rather rapidly during the early puerperium.
3. Cord blood is uniformly higher in total calcium content than maternal blood, but the relative proportion of diffusible calcium is considerably lower.
4. Abnormal pregnancies show variations in both the total and diffusible calcium, not only in the mother but also in the child.
5. A possible connection between the serum calcium and the presence of toxic amines in the blood of eclamptics, involving a disturbance in the function of the parathyroids, is suggested.

We gratefully acknowledge the valuable assistance rendered by the internes of the Hermann Hospital in this investigation. We also wish to express our appreciation to Dr. E. D. Plass, for his helpful criticism of the manuscript.

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VARIATIONS IN SERUM CALCIUM AND PHOSPHORUS DURING PREGNANCY

I. NORMAL VARIATIONS

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IN ORDER to determine the variations in serum calcium and phosphorus that might occur normally in healthy women during pregnancy, we believed that it would be necessary not only to examine a large number of women, but to make repeated examinations upon the same women. With this in view, we have made some 4,896 calcium and phosphorus determinations upon 900 patients in our prenatal dispensaries. Those patients were selected who had come to the clinics earliest in their pregnancies and who showed a willingness to cooperate. They were followed throughout the course of pregnancy, with analyses being made at the time of each visit to the dispensary. Since our object was to obtain the normal or average figures, no effort was made to control the diet or habits of the patients other than that made routinely by the dispensary.

PROCEDURE

Determinations were made in the same manner as formerly.^{1,2} The calcium was precipitated directly from the serum with ammonium oxalate. The precipitate was allowed to stand overnight at from 0° to 5° C., then centrifuged down and washed with ice cold 2 per cent ammonium hydroxide. It was then dissolved in normal sulphuric acid and titrated with hundredth normal potassium permanganate. The permanganate was standardized daily, the standardization providing an end point for the particular intensity of light in which the determinations were made. Blanks for the sulphuric acid were subtracted. Frequent checks, as described previously, indicated an accuracy of within 1 to 2 per cent.

Phosphorus was determined colorimetrically by a slightly modified form of the Kuttner and Lichtenstein method.³ The stannous chloride was added to the standards

and unknowns with constant stirring, the addition being made to the entire day's series within the space of ten minutes. The color was allowed to develop for twenty minutes before reading. Sufficient standards were provided so that readings could be made within plus or minus 3 mm. of the standard, set at 20 mm. Readings were completed within two hours. Checks, run as before, indicated a possible error of approximately 5 per cent.

Although some women were followed over a period of thirty-six weeks, the most of our determinations fell within the interval of thirty-two weeks before delivery to eleven weeks postpartum. For convenience this time was divided into intervals of one, two, and three weeks preceding or following delivery, corresponding to the frequency of the routine dispensary visits, which were made more often as the subjects approached term. Determinations on all patients falling in the same interval were averaged together.

RESULTS

In order to investigate the possibility of seasonal variation, the determinations for each of these intervals were divided into 12 groups, according to the month in which the blood was drawn. The monthly averages for each interval were then plotted against time in months. In the case of the calcium, the resulting plots showed that in every interval, especially those before delivery, there was a definite sag during the earlier months of the year. On this basis we divided the year into two parts: the first, including the months January to May, were characterized by low values; the second, including June to December, by high. The phosphorus results did not show this seasonal variation.

There is also a definite lowering due to pregnancy. These two effects, each of which probably influences the other, are illustrated, for calcium, in Fig. 1. The upper line indicates for each interval the averages of the determinations made during the months June to December, inclusive. The lower, the averages for the January to May period. The numbers indicate the number of determinations made during the indicated interval. The slight but consistent fall in both curves from the values of 10.58 mg. and 10.05 mg., respectively, for the interval of twenty-nine to thirty-two weeks before delivery, to those of 9.87 mg. and 9.61 mg. at six to seven weeks before delivery, is due to the pregnancy. From this point until the last week before delivery there is almost no change in the upper curve, but a small steady rise in the winter curve to 9.76 mg. The first week following delivery the averages reach 10.26 mg. and 10.24 mg., respectively. The second week they are still higher, 10.40 mg. and 10.49 mg., having crossed. From five to seven weeks postpartum the values are 10.44 mg. and 10.25 mg., and at from eight to eleven weeks they are 10.41 and 10.44 mg. These postpartum values compare favorably with the original findings of the higher group. This would indicate that the greatest demand for calcium made on the maternal system comes during the period of from four to seven weeks preceding delivery, and that upon removal of the fetus, recovery follows immediately.

Although the majority of our subjects nursed their babies, there was no lowering of the serum calcium averages during our period of observation. On the contrary, the lactating group averaged somewhat higher than the others; for example, in the January to May group at from five to seven weeks 166, or 84 per cent, were nursing, with an average of 10.26 mg. as opposed to 10.25 mg. for the whole group. At from eight to eleven weeks 22, or 71 per cent, were nursing, with an average of 10.51 mg., as opposed to 10.44 mg. for the whole group. Similarly, in the June to December group, at from five to seven weeks there were 155, or 80 per cent nursing, averaging 10.46 mg. as against 10.42 mg., while at from eight to eleven weeks 34, or 87 per cent nursing, averaged 10.42 mg. The whole group averaged 10.41 mg. In every instance the nursing group had higher calcium values than the supplemented or nonnursing group.

Although the actual numerical changes due to pregnancy are very slight, they are significant. This is illustrated in Table I, where the early prenatal and the later postpartum findings are compared with the low values found at from six to seven weeks before delivery. These changes, varying between 0.34 mg. and 0.83 mg., are from 8 to 20 times the probable error of the difference. The differences between the two curves are likewise significant throughout the entire prenatal curve, as shown in the lower portion of the table. Following delivery, however, the significance is lost. During the second week postpartum the curves cross, and while the difference found from five to seven weeks postpartum is some 5.7 times as great as the probable error of the difference, that during the next interval, from eight to eleven weeks, is again negative. This convergence and crossing of the curves following delivery, with the loss of significant differences, leads us to the belief that quite possibly the seasonal difference is accentuated by the condition of pregnancy, and that it might be very difficult to demonstrate it in normal nonpregnant women. This belief is also indicated by our own failure to demonstrate it in our study of normal serum calcium.²

It should not be overlooked that not only are the findings made during the January to May period lower than those made during the remaining months, but that with the exception of the early prenatal findings made during the second months of pregnancy, they are below the lower limits of the normal range, which we have found to be 10.0 mg. to 11.5 mg. per 100 ml., throughout the whole term of the pregnancy. Determinations made during the June to December period do not dip below the lower limits until the eleventh to the thirteenth week before delivery, although the average never rises above the lower third of the normal range.

The favorable comparison of the final postpartum averages with the early prenatal findings is borne out by an individual study of some of

TABLE I. SIGNIFICANCE OF SERUM CALCIUM CHANGES DURING PREGNANCY

INTERVAL WEEKS FROM DELIVERY		JANUARY TO MAY (INCLUSIVE)				CHANGE				
		NO. CASES	AV. MG. PER 100 ML.	PROBABLE ERROR OF THE MEAN	INTERVAL WEEKS FROM DELIVERY	NO. CASES	AV. MG. PER 100 ML.	PROBABLE ERROR OF THE MEAN	DIFF. MG. PER 100 ML.	PROBABLE ERROR OF THE DIFF.
JUNE TO DECEMBER (INCLUSIVE)										
Prenatal	29-32	30	10.05	0.047	Prenatal	6-7	9.61	0.017	0.44	0.052
Prenatal	26-28	58	9.95	0.036	Prenatal	6-7	9.61	0.017	0.34	0.040
Postpartum	5-7	192	10.25	0.018	Prenatal	6-7	9.61	0.017	0.64	0.025
Postpartum	8-11	31	10.44	0.060	Prenatal	6-7	9.61	0.017	0.83	0.063
JUNE TO DECEMBER (INCLUSIVE)										
Prenatal	29-32	30	10.58	0.050	Prenatal	6-7	9.87	0.020	0.71	0.052
Prenatal	26-28	49	10.39	0.039	Prenatal	6-7	9.87	0.020	0.52	0.040
Postpartum	5-7	195	10.44	0.022	Prenatal	6-7	9.87	0.020	0.57	0.030
Postpartum	8-11	39	10.41	0.043	Prenatal	6-7	9.87	0.020	0.54	0.047
JUNE TO DECEMBER										
JANUARY TO MAY		JUNE TO DECEMBER								
		JANUARY TO MAY				JUNE TO DECEMBER				
Prenatal	29-32	30	10.05	0.047	Prenatal	29-32	10.58	0.050	0.53	0.069
Prenatal	26-28	58	9.95	0.036	Prenatal	26-28	10.39	0.039	0.44	0.050
Prenatal	6-7	247	9.61	0.017	Prenatal	6-7	9.87	0.020	0.26	0.026
Postpartum	5-7	192	10.25	0.018	Postpartum	5-7	10.44	0.022	0.19*	0.033*
Postpartum	8-11	31	10.44	0.060	Postpartum	8-11	10.41	0.043	-0.03†	0.070†

*Probably not a significant difference.

†Not a significant difference.

the patients observed over longer periods which show that while for the most part the postpartum values do not quite equal the earliest prenatal figures, they closely approximate them. Twenty-eight patients were followed from the first or second month of pregnancy to the second or third month postpartum, 2 to the fourth, 1 from the third month of pregnancy to the third month postpartum, and 1 to the fourth. In 11 instances where both of these extremes fell in the group of the summer months, June to December, only 3 of the postpartum values equaled the prenatal. In 4 where both came in the January to May period, only one postpartum value was higher. Even when the prenatal determination was made in the winter and the postpartum in the summer, only 10 out of 16 showed the latter figure higher.

The effect of recent pregnancies was also observed. In 10 cases where determinations were made in either the first or second month of preg-

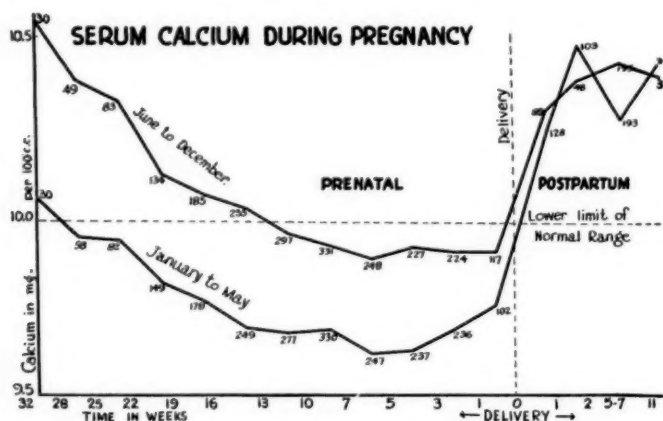


Fig. 1.—The curves illustrate the seasonal variation and alterations in serum calcium during pregnancy. The numbers indicate the determinations made in each interval, the average of which is plotted. No determinations were made between the end of the second week and the beginning of the fifth week postpartum.

nancy on women who had had a previous delivery within eighteen months or less, three within a year, only 2 were low as compared with the general averages. But when the values found were compared against those of the same woman during her previous pregnancy, there was a difference. Twenty-eight patients, varying from para i to para x and in age from thirteen to thirty-seven years, were followed through two successive pregnancies, averaging fourteen months between deliveries. Three hundred and six determinations were made. Seventy-five pairs of these fell in the same interval of successive pregnancies, giving directly comparable figures. In only 17 of these 75 instances were the values of the latter pregnancy equal to or better than those of the former, and 5 of these were summer values compared with winter. In 16 other instances the later determinations made during the summer failed to equal those of the earlier pregnancy made during the winter, although

summer averages are distinctly higher than those of winter. The trend of the remaining 156 determinations, which had no directly corresponding determination made during the other pregnancy, confirms this lowering in all but 4 cases, the same 4 supplying most of the exceptions among the matched determinations. There is, therefore, strong evidence to indicate that there is a slight lowering of the level of the serum calcium of a patient through close successive pregnancies.

The averages of the phosphorus determinations are given in Fig. 2. Since there was no indication of seasonal differences, all have been included in the one curve. Here again the effect of the pregnancy is seen in the gradual decline from 3.53 mg. at from twenty-nine to thirty-two weeks before delivery to the low point of 3.24 mg. at from eleven to thirteen weeks before delivery.

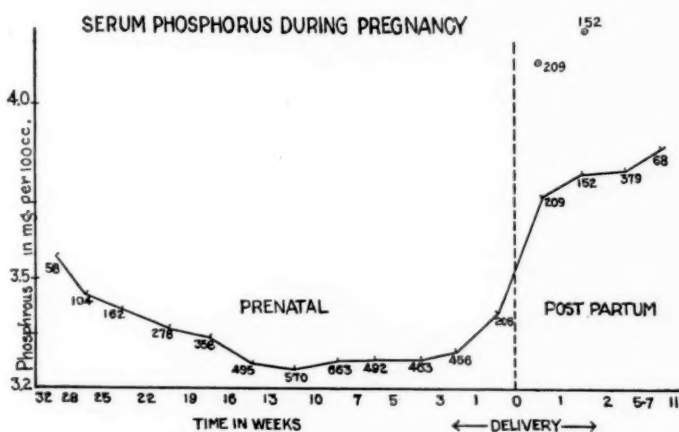


Fig. 2.—The curve illustrates the fall and recovery of the inorganic phosphorus of the serum during pregnancy, with the sharp increase following delivery. The numbers indicate the determinations made in each interval, the average of which is plotted. The two isolated points in the first and second weeks postpartum are values uncorrected for the effect of carbohydrate metabolism. No determinations were made from the end of the second to the first of the fifth week postpartum.

teen weeks. The small difference, 0.20 mg., is 6.2 times the probable error of the difference. During the remainder of the pregnancy there is a gradual recovery until the final week when the value is almost identical with the first figure. Following delivery there is an abrupt rise. These determinations, made in the hospital, were on blood specimens drawn before breakfast, and are therefore not directly comparable with the rest of the series. From a study of 270 normal determinations, made before and after eating, we have found an average fall of 9 per cent in the phosphorus due to carbohydrate metabolism under the circumstances encountered. We have applied this correction to our figures, lowering the averages from 4.16 mg. and 4.23 mg. found the first and second weeks postpartum, to 3.74 mg. and 3.81 mg. These values fit in well with the succeeding dispensary figures, 3.82 mg. at from five to seven

weeks and 3.87 mg. at from eight to eleven weeks. The rise to these points is markedly significant, since the differences between them and the low point, eleven to thirteen weeks before delivery, while only 0.38 mg. and 0.63 mg., respectively, are 24 and 12.9 times the probable error of these differences.

If we could apply the 9 per cent correction previously mentioned to the entire curve, our figures would be more comparable to other reported data, but we have refrained from doing so because we have as yet no proof that a correction for nonpregnant women can be applied to pregnant women. The present curve illustrates satisfactorily the early fall in phosphorus, with recovery during the latter part of the pregnancy, and a marked increase following delivery. This postpartum increase, like that of the calcium, was not affected by nursing during our period of observation.

At from five to seven weeks 311 of the subjects, or 82 per cent, were found to be nursing. These had an average of 3.87 mg. per 100 ml., as against 3.82 mg. for the entire group. At from eight to eleven weeks 50, or 77 per cent, were nursing, with an average of 4.11 mg., as against 4.05 mg. for the whole. Only a few cases were observed later, but of the 13 examined between the twelfth and fifteen week postpartum 11 were nursing, with an average of 3.92 mg. as opposed to 3.85 mg. for the 13.

Unlike calcium, phosphorus does not show the lowering effect of rapid successive pregnancies. This may be due to the greater individual variation of the phosphorus values, which hide the tendency, or it may not exist. In either case our results do not show any consistent lowering. In the 28 cases of successive pregnancies studied, 33 out of the 75 directly comparable determinations were higher for the later pregnancy, and in all the other cases where early determinations were made on women having recently undergone previous pregnancy, no consistent trend could be discovered.

SUMMARY

During pregnancy there is a distinct seasonal difference in the serum calcium, since blood specimens drawn during the months January to May, inclusive, average less at every stage of the pregnancy than those drawn during the remaining seven months. Following delivery the difference tends to disappear.

There is also a significant decline in the calcium, approximately 5 per cent, due to the pregnancy itself up to six or seven weeks before delivery; then a slight rise until delivery, followed by a sharp increase. The postpartum values remained high, approaching the early prenatal, even with nursing, until the end of the study, from eight to eleven weeks postpartum.

Close successive pregnancies tend further to lower the serum calcium level of the individual during subsequent periods of gestation.

Phosphorus showed no seasonal variation, but due to the pregnancy itself there was a significant fall in the average values, about 6 per cent, until the eleventh to the thirteenth week before delivery, followed by an equal rise until term. Immediately following delivery there was a sharp rise, 19 per cent, to higher values than those observed at the beginning of the study, from twenty-six to twenty-eight weeks before delivery. These high values were maintained until the dismissal from eight to eleven weeks postpartum.

There was no evidence of a lowered phosphorus level as a result of previous pregnancies.

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PRIMARY BREECH PRESENTATIONS

A STUDY OF 550 CONSECUTIVE DELIVERIES IN THE CLEVELAND MATERNITY HOSPITAL, 1923-1932

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THE conduct of breech labor and the technic of delivery are still imperfect and inadequate. The fetal mortality and morbidity are considerably greater than those of any other presentation. In order to determine the relative merits of the various methods of management and delivery, we have studied the breech presentations at the Cleveland Maternity Hospital from January 1, 1923 to March 31, 1932. During this time there were 16,166 deliveries of which the 550 breech presentations form the basis of this report.

The methods commonly employed at the Cleveland Maternity Hospital are at variance with those in use at many other clinics. A critical study of our results has therefore been made and comparisons resorted to in order to justify or discredit the technic, as a common basis of comparison in statistical studies is difficult to obtain; our results are therefore quoted in full. During the period with which this paper is concerned, many notable contributions have been made to the study of breech presentations. Rasmussen,¹ Westman,² Irving and Goethals,³ Taussig,⁴ Mohler,⁵ Caldwell and Studdeford,⁶ King and Gladden,⁷ Ryder,⁸ Pierson,⁹ McGuinness,¹⁰ Gibberd,^{11, 12} Bourne,¹³ Dunbar,¹⁴ Ridler,¹⁵

TABLE I

AUTHOR	METHOD OF DELIVERY	TOTAL NO. CASES	GROSS FETAL MORTALITY %	CORRECTED FETAL MORTALITY %	FETAL MORTALITY IN P.P. %	FETAL MORTALITY IN M.P. %	REMARKS
Rasmussen	Varied	465	14.2	-	18.8 gross	6.7 gross	No mortality where there was no indication for immediate delivery; 18.4% where such indications existed.
Westman	Expectant where possible	893	-	8.8	11.2 corrected	5.2 corrected	Excluded fetuses under 2,000 gm. or cases in which disease of mother or fetus reacted unfavorably upon the outcome.
Irving and Goethals	A—Expectant B—Delivery with full dilatation by extraction	235 30	9.78 corrected 6.6	-	12.7 corrected	7.8 corrected	Excluded twins, prematures, maceration, accidental complications, etc.
Taussig	Expectant where possible	162	-	10.5 corrected	12.0 corrected	8.8 corrected	Report includes only deliveries at full term.
Moller	Varied	170	35.4	7.6 corrected	6.4 corrected	8.3 corrected	These figures exclude prematures; also macerated and syphilitic fetuses.
Caldwell and Studdelford	Spontaneous. Noninterference as far as possible	348	14.0	11.1	8.3	20.0	Deliveries done by 18 different operators, the less experienced handling multiparas.
King and Gladden	Extraction under anesthesia	158	-	10.1	7.7	12.5	This excludes babies under 5 lb., macerated fetuses, and twins. Delivery at full dilatation in frank breech and footlings; extraction when buttocks present in full breech.

TABLE I—Cont'd

AUTHOR	METHOD OF DELIVERY	TOTAL NO. CASES	GROSS FETAL MORTALITY %	CORRECTED FETAL MORTALITY %	FETAL MORTALITY IN P.P. %	FETAL MORTALITY IN M.P. %	REMARKS
Ryder	Varied	59	15.2	5.0	—	—	There were 52 viable infants in this series; 49 of which were seen before the onset of labor, and 17 of these were delivered as breech without mortality. There were 3 cases seen after the onset of labor, 2 being stillborn after breech delivery. That is, there were 2 fatalities in 19 breech deliveries or 11.2%.
Pierson	Varied	142	—	12.0	—	—	
McGuiness	Not reported	104	32.7	19.8	13.3	23.2	Subsequently he had 62 such presentations upon which he did cephalic versions with 1 fetal death due to toxemia in the mother.
Gibberd All London hospitals	Not stated Uncomplicated Complicated	269 218	26.0 43.0				Excludes prematures, macerations, etc.
Guy's Hospital	Uncomplicated, 209 Complicated, 50 Twins, 79	338		21.5 53.0 21.0	28.0 57.0 33.0	15.0 49.0 9.0	
Gibberd	Unstated	221	23.3	—	31.5	15.0	He reports 204 cases treated by cephalic version with 2% mortality plus 1.5% neonatal deaths.

TABLE I—CONT'D

AUTHOR	METHOD OF DELIVERY	TOTAL NO. CASES	GROSS FETAL MORTALITY %	CORRECTED FETAL MORTALITY %	FETAL MORTALITY IN P.P. %	FETAL MORTALITY IN M.P. %	REMARKS
Bourne	Breaking up frank breech before descent into pelvis, allowing delivery to proceed spontaneously	—	9.5?	—	11.0	8.0	Details methods of assisting but does not state procedures adopted routinely.
Dunbar	Varied	135	12.6	9.7	9.78	9.78	Excludes macerated fetuses and monstrosities. Does not practice cephalic version.
Ridler	District nurses' spontaneous deliveries Hospital cases: Nurses Internes	106 329 97	13.0 18.2 22.7	1.13 3.44 15.3	13.9 — —	9.5 — —	Method of delivery unstated. Internes probably delivered more difficult cases.
Wilson	Spontaneous to umbilicus	37	8.1	—	—	—	All delivered by residents.
Greene	Not stated	258	32.5	6.2	—	—	Excludes prematures (under 5 lb., or 8 months), macerated fetuses, monstrosities, etc.
Grier	Not stated	177	20.0	7.0	—	—	Excludes prematures (those 7½ months and under), monstrosities, and macerated fetuses.
Cameron	Not stated	64	12.5	?	?	?	Fetuses which weighed 1,500 gm. or over were considered viable.
Morton	Varied, usually breech extraction	(301) 256 were viable	14.8	9.1	?	?	

Wilson,¹⁶ Greene,¹⁷ Grier,¹⁸ Cameron,¹⁹ and Morton,²⁰ have reported the results of such presentations at their respective clinics. The fetal mortality varied considerably, the gross mortality being high in almost all instances, whereas the corrected mortality varied with the standard used. The statistics reported during this period are given in Table I.

It will be seen from these figures that the gross fetal mortality varied from 43 per cent to 8.1 per cent, while the corrected rate was from 21.5 per cent to no mortality. The mortality was higher in primiparous patients in 9 of 13 reports in which they were compared, and varied from 57 per cent to 6.4 per cent. The rate in multiparas varied from 49 per cent to 5.2 per cent. In those instances in which the mortality was higher in multiparas it was explained that the average weight of the babies was greater, or that less skilled attendants had delivered them.

Since the epoch-making paper of Holland²¹ in 1922, the cause of death in many breech labors has been made clear. The work of Crothers,²² Pierson,⁹ Lindsay,²⁴ Ford,²⁵ Fahmy and Crowe,²⁶ Cameron,¹⁹ Greene,¹⁷ and others, has done much to consolidate the view that injury rather than intrauterine asphyxia due to compression of the umbilical cord is the cause of most fetal deaths. The mechanics of breech delivery with the resultant strains and stresses upon the craniovertebral cavity have been fully explained by Holland, Crothers, and others. Attention has been drawn to spinal cord injuries in breech deliveries and the work of Lindsay,²⁴ Ford,²⁵ and Crothers²³ should serve to stimulate a more careful study of infants following breech delivery. The incidence of paraplegia compatible with life is probably greater than is realized at present. The factor which breech presentations play in their production has been noted by the above mentioned writers and suggestions for their prevention put forth. The greater use of external cephalic version is unquestionably the most useful procedure in the prevention of breech mortality. Its use and technic, with improved results, have been carefully reported by Gibberd,¹² Bartholomew,²⁷ Ryder,⁸ McGuiness,¹⁰ and others. The use of forceps to the aftercoming head is advocated by Piper²⁸ and others in order to prevent fetal strains and flexions incident to manual extraction. In addition to some specific alterations in technic which are advocated by different persons, all writers emphasize the necessity for gentleness and deliberation in delivery as the two requirements for reduction in fetal mortality.

Management of Breech Labor and Delivery at Cleveland Maternity Hospital.—Deliveries at this hospital are conducted by members of the staff, resident obstetricians, and other reputable physicians who may desire to deliver their patients there. The greater proportion of the patients are under the care of the staff and resident obstetricians. These patients are treated in the following manner: No interference is tolerated in the first stage unless fetal or maternal distress necessitates some action being taken. During labor, primiparas are kept comfortable under

morphine and scopolamine treatment, with supplementary colonic or inhalation ether analgesia; multiparas receive sodium amytal by mouth with similar supplementary analgesia. As soon as full dilatation occurs, complete anesthesia is obtained by ether or gas. The patient is then placed across the delivery bed and supported in a modified Walcher position by two assistants. After scrubbing with sterile green soap and water, an iodine alcohol preparation of the vulva and perineum is done, and the patient draped with sterile towels. The perineum, vagina, cervix, and lower uterine segment are thoroughly ironed out manually, and preliminary episiotomies are done in those cases which warrant it. All presentations are converted into double footlings, and extraction is carried out in a deliberate, careful, and gentle manner. The feet are grasped at the ankles and gentle traction is made upon them until the legs are exposed slightly above the knees when greater traction is applied to the anterior leg so that the breech sits in the hollow of the sacrum in its natural position. At this point an episiotomy should be done if necessary. As traction proceeds, the back rotates anteriorly beneath the symphysis pubis and a warm moist towel is placed about the lower extremities as the hips are expelled from the vulva. This facilitates traction and prevents the stimulation of respiratory movements on the part of the fetus. Traction is now made either from the ankles or hips, the body of the infant being kept in about the same plane as the vagina until the scapulae can either be seen or felt. Gentle rotation of the child's body then delivers one shoulder, and reversed rotation with the first arm held alongside the body delivers the second arm and shoulder. Manual assistance with the forefinger acting as a splint along the arm, is sometimes helpful or necessary in completing the delivery of the shoulders. We consider it of vital importance that no rotation be attempted until the scapulae are well exposed or can be felt easily. Earlier, hasty attempts at rotation or delivery almost invariably result in extension of the arms, with resultant complication of delivery. Having delivered the shoulders, the body is placed with the legs straddling the operator's forearm. Gentle traction is now made upon the jaw, with the forefinger in the mouth in order to facilitate flexion of the head, which is simultaneously rotated into the right or left oblique diameter, depending upon the preference of the operator. Using careful but fairly constant traction, combined with equally cautious suprapubic pressure, the delivery is completed. As soon as the nose and mouth are exposed, the mucus is removed from the airway and the perineum is carefully protected from extensive lacerations. At no time is delivery unduly hastened, nor rough, sudden manipulation introduced. It is our endeavor to await full dilatation of the cervix, carefully iron out the vagina and perineum, then accommodate the fetal axes to the pelvic axes and avoid dangerous traction or torsion in the delivery. We have found that forceps to the after-coming head are rarely necessary, although they may unquestionably facilitate delivery in some instances.

REPORT OF CASES

There were 16,166 consecutive deliveries at the Cleveland Maternity Hospital in the years 1923 to 1932, of which 550 were breech presentations, an incidence of 3.4 per cent. There were 332 primiparas and 218 multiparas. In the 471 instances in which the type was recorded, there were 302 frank, and 18 full breech, 109 double and 42 single footlings. In the 442 cases in which position was reported, there were 177 L.S.A., 66 L.S.P., 129 R.S.A., and 70 R.S.P. The average duration of labor for all primiparas was fifteen hours, for all multiparas twelve hours. In cases in which there was premature labor, or the first coming

of twins was a breech, the duration of labor was thirteen and a half hours for primiparas and twelve hours for multiparas. The effect of the preservation of membranes upon the duration of labor was not marked; in early rupture the duration of labor was fifteen hours for the primiparas and twelve hours for the multiparas. In instances where the membranes ruptured at or after full dilatation, the duration of labor was sixteen hours in the primiparas and thirteen hours in the multiparas.

Maternal Mortality and Morbidity.—There were 213 perineal lacerations reported, 115 first degree, 98 second degree, and no complete tears. Twenty-five cervical lacerations were recorded and episiotomies were done in only 30 cases. Thirty-nine mothers or 7.1 per cent had a temperature of 38° C. or higher for two successive days postpartum, not including the first day. The causes recorded were as follows: pyelitis 5, pyelitis and cystitis 1, retained secundines 4, respiratory complications 9, breast infections 2, pelvic inflammatory diseases 2, cellulitis of the foot 1, undetermined 15.

There were 3 maternal fatalities or 0.55 per cent. The cause of death in these cases was (1) thyroid storm, following cesarean section; (2) lobar pneumonia and lung abscess, following a vaginal delivery in a mother who had a badly failing heart on admission; and (3) eclampsia, in a six-and-a-half-month pregnancy where vaginal delivery of twins had been done. All deaths occurred where pregnancy had been a complicating factor, but in none of them can the death be attributed to the breech presentation.

Fetal Mortality, Morbidity, and Accidents of Labor.—In this series of 550 breech presentations, there were 62 twins, and a total number of 562 infants were delivered. There were 108 stillbirths or neonatal deaths, a gross mortality of 19.2 per cent. Excluding prematures, macerated fetuses, and those with abnormalities incompatible with life, there were 34 viable full-term infants stillborn or died prior to discharge from the hospital, a corrected mortality of 6 per cent. Fifteen infants survived delivery and left the hospital, although they showed signs of cerebral hemorrhage or other cerebral irritation. Four of these occurred in multiparas, 11 in primiparas. Five were reported as easy deliveries, 8 were difficult, and in 2 no history of delivery was obtained. The symptoms reported and their frequency are as follows: cyanosis 9, twitching 8, rigidity 2, convulsions 2, shrill cries 2, icterus 2, and bloody vomitus 1.

In only one case was a follow-up reported, and that infant appeared normal at the end of one year.

Fetal injuries were recorded in 9 other living infants or 1.6 per cent. These were as follows: dislocation of clavicle 1, fracture of clavicle 2, fracture of humerus 2, and peripheral paralysis 4.

Two of the latter cases made complete recovery prior to discharge. The others were unimproved at the time they left the hospital. In the accidents of labor which were reported, there were 6 prolapsed cords, and 10 cases with hemorrhage due to premature separation of the placenta in 3 instances, and to placenta previa in the remaining 7 cases.

Method of Delivery and Operative Procedures.—Five hundred and sixteen were delivered as double footlings by breech extraction, 11 as single footlings, 3 as frank breech, 13 by cesarean section, and 7 were delivered spontaneously. All of the latter were macerated or premature. Manual dilatation of the cervix was performed 32 times. The indications recorded for this procedure are listed as follows: irregularity of the fetal heart indicating the necessity of terminating labor 4, no progress in labor with a partially dilated cervix 9, a combination of these indica-

tions 2, prolapsed cord 3, eclampsia or toxemia without convulsions 2, maternal exhaustion 2, early lobar pneumonia 1, bleeding 2, polyhydramnios 1, cervix almost fully dilated and dilatation easily completed 3, and no indication was recorded in 3.

Voorhees' bags were inserted 12 times with the following indications: past term when medical induction of labor had failed 2; prolonged labor, slow or arrested dilatation 6; marginal placenta previa at 5½ months 1; severe toxemia with convulsions at 5½ months 1; induction at thirty-seventh week because of loss of previous pregnancy at term 1; cause unstated 1.

Craniotomy was performed 3 times, the indication being hydrocephalus in each instance.

Cesarean section was the method of delivery in 13 cases for the following indications: previous section 4, placenta previa 3, desire for living baby 3, occlusion of cervix (Porro section) 1, relative disproportion and cervical dystocia 1, eclampsia with convulsions 1.

The group in which the indication was stated to be "Desire for living baby" was made up of 2 multiparas, forty-two and thirty-nine years of age respectively, who had had difficulty with previous pregnancies and were without living children; and 1 primipara thirty-nine years of age. There was one maternal death as a result of thyroid storm, nine days postpartum. Three patients, including the one who died, ran a morbid postoperative course. There was no apparent cause in one case, the other had an infected abdominal incision. Episiotomies were performed in only 30 cases.

Factors Responsible for Breech Presentation.—The factors which seemed responsible for breech presentation in the greater number of cases were prematurity, maceration, gross fetal abnormalities, and contracted pelvis. No uterine abnormalities were recorded which could in themselves be responsible for the presentation. The incidence of fetal abnormalities was 15 or 2.7 per cent. There were 28 macerated fetuses or 4.9 per cent, and 119 prematures or 21.1 per cent. The high incidence of these complications, 28.7 per cent of breech presentations, accounts for the high gross mortality. The corrected rate, however, is still much higher than that in other presentations.

Consideration of Full-Term Deaths.—Arbitrarily considering all infants weighing 2,500 grams or over as full term, and excluding macerated and congenitally deformed fetuses, there were 400 full-term infants delivered. There were 34 full-term stillbirths or neonatal deaths. That is, 8.5 per cent of the viable infants failed to survive delivery or the accidents associated with labor. Excluding cases in which there were accidents of labor, such as prolapsed cord, placenta previa, toxemia in the mother, etc., there were 27 full-term deaths or a mortality of 6.75 per cent. There were 28, or 7 per cent, in primiparas, and 6, or 1.5 per cent, in multiparas. The mortality in primiparas is considerably higher than in multiparas which is the common finding. Caldwell and Studdeford believe that there is greater risk in the multiparous cases. In our experience, delivery is unquestionably more difficult in primiparas. The resistance of the soft parts is greater and the difficulties of extraction are correspondingly increased. The more frequent use of episiotomy would, in part, obviate this difficulty, but the resistance in the upper portions of the birth canal remains unchanged. This applies particularly to the lower uterine segment which is always more resistant and tense in primiparas. Seven of the primiparas were thirty years of age or older. There were 55 primiparas in the series in this age group. That is, 12.7 per cent of such cases lost full-term babies due to delivery or accident of labor. There were 277 primiparas under thirty years of age and 7.2 per cent lost full-term infants. It is obvious that elderly primiparas run an increased risk of stillbirth in breech presentations. Early rupture of the membranes

was reported in 4 of these 7 cases. The findings here are in accordance with the reports from other clinics. We believe that where there is any question of disproportion, cesarean section is the method of choice in elderly primiparas.

The Relation of Type, Position, and Weight to Stillbirths or Neonatal Deaths.—The type of presentation was reported in 28 of the 34 full-term deaths, of which 78.5 were frank, 10.8 double, and 10.7 single footlings. None was full breech; only 1 stillbirth is reported in the whole series in those cases presenting as a complete breech, and it was a monstrosity. This corroborates Taussig's findings that the greater diameters of full breeches make better dilators and therefore occasion less difficulty in delivery. The position of the fetus is reported in 27 cases with R.S.A. 51.8 per cent, L.S.A. 33.3 per cent, and R.S.P. 14.9 per cent. This is in contrast to the positions reported in the whole series in which there were 29 per cent R.S.A., whereas L.S.A. positions formed 40 per cent of the total. There does not seem to be any relationship between fetal mortality and position. The weight of the fetus was recorded in 10 primiparas with an average of 3,078 gm. and in 4 multiparas with an average of 2,954 gm. The average weight of the other full-term primiparous infants was 3,235 gm. and that of multiparous babies was 3,354 gm. Thus the average weight of the stillborn babies was less than that of living children. This seems to indicate that the weight of the fetus has little to do with stillbirth. It is obvious that a heavier child may provide greater difficulty in delivery than one of normal weight. We cannot, however, subscribe to the view that the weight of the fetus rather than the age or parity of the mother is the important factor in the production of stillbirths.

Duration of Labor, Rupture of Membranes and Their Effect Upon Stillbirths.—Contrary to the majority of reports, we did not find that the duration of labor was prolonged in breech presentations. This is in part explained by the shorter second stage which these patients had, but part, we believe, is due to the use of analgesia in the first stage. The provision of adequate relief from pain seems to hasten definitely the progress of labor. We cannot agree with the authorities who decried the use of sedatives in breech labor, any more than with those who withhold it in other presentations, as in our experience it neither increases the duration of labor, nor the risks of delivery. The duration of labor was reported in 33 cases in which viable infants were lost. The average duration of labor in the primiparas was twenty-two hours, and in the multiparas, twenty-one hours. The duration of labor was not materially affected by the early or late rupture of membranes. The average duration of labor in primiparas with early rupture of membranes was twenty-four hours, with late rupture twenty-three hours. The time of rupture was reported in only 2 multiparas, the duration of labor being seventeen hours in the case with the late rupture of membranes and seven hours in the one with early rupture. The average duration of labor in these cases is about one-half to one-third greater than the average duration of labor where all cases were considered. The importance of the preservation of membranes in the prevention of stillbirth is apparent when we consider that in the 34 full-term deaths there were 20 cases or 58.8 per cent in which the membranes ruptured early; whereas 6 or 17.6 per cent are reported to have ruptured late in labor. The time of rupture in the remaining cases was not reported.

Cause of Death.—Postmortem reports were available in 6 cases, in which 4 presented tentorial tears and intracranial hemorrhage and 2 showed atelectasis. Cerebral irritation was present clinically in 6 other cases, while asphyxia neonatorum was diagnosed in 2 cases. There were no instances reported of broken necks. The series of postmortems is so small that no conclusions can be drawn from it as to the frequency of the latter injury.

Complications of Delivery and Labor, Including the Operative Procedures Adopted.
—Difficulties in delivery and complications of labor were recorded as follows: difficult deliveries 18, due to cervical dystocia 9, bony dystocia 5, perineal delay 4, prolapsed cord 3, premature separation of placenta (no fetal heart heard in 2) 3, placenta previa (marginal) 1, toxemia of pregnancy 3, and extended arms 5. There were 16 cases in which delivery was easily accomplished. In 7 of these, no maternal or obstetric complications were present.

The deaths here are comparable in part with those occurring in cephalic presentations without obvious cause. There were only 6 cases with prolapsed cords in the whole series and the mortality was 50 per cent, which, according to Caldwell and Studdeford,⁶ is a much higher figure than that in cephalic presentations. The treatment adopted was usually manual dilatation of the cervix. In at least 2 of these cases, the cord had ceased pulsation before they entered the hospital or delivery was begun. The wisdom of manual dilatation in such cases is dubious, and the results obtained suggest that replacement, position, and the use of the Voorhees' bag might yield better results.

At least 2 of the 5 cases in which bony dystocia was reported, should have had sections. The disproportion was so great that cephalic delivery would probably have been impossible. The wisdom of attempting a vaginal delivery in the face of possible disproportion is questionable. The dangers of delivery are such that the patient may become a permanent invalid and in any event may never become pregnant again, even if no fetal mortality results from vaginal delivery.

The operative procedures adopted to facilitate delivery were as follows: Voorhees' bag 3, manual dilatation of cervix 8, episiotomy 4.

Of the 32 instances in which manual dilatation of the cervix was performed, 8 full-term fatalities resulted. That is, 23.5 per cent of the full-term deaths occurred in these cases. The difficulties in obtaining satisfactory dilatation and paralysis of the cervix by manual methods are emphasized by these figures. We have no recorded instance of incision of the cervix in this series. It might be preferable to the former procedure where dilatation is not satisfactory and immediate delivery is required. The small number of episiotomies was based upon the presumption that manual dilatation of the perineum was sufficient in the majority of cases to permit easy delivery. It is, however, unsatisfactory if complications occur, and we feel now that all full-term primiparous breeches should have episiotomies done prior to extraction or when the breech reaches the perineum in the delivery.

DISCUSSION

The results reported from this series of cases are not remarkable nor do they differ materially from those reported elsewhere. They serve to prove that no single method of delivery is completely successful in removing the danger of uncomplicated breech deliveries. The more frequent use of external cephalic version is undoubtedly the best way of lowering the mortality in breech presentations. There were only 12 recorded attempts at this procedure in our series, but unquestionably many more were made without being recorded. The excellent results reported by Gibberd,¹² Ryder,⁸ Bartholomew²⁷ and McGuiness,¹⁰ are such that the general adoption of their method is to be recommended. The results obtained here are not sufficiently remarkable to warrant any change being made in our procedures. We still believe that the majority of breech presentations are better delivered upon full dilatation of

the cervix. This largely eliminates the dangers of premature separation of the placenta, contraction rings, and impaction of the frank breech in the pelvis. The more careful consideration and study of all breech presentations should serve to eliminate many fetal deaths such as occurred in this series. The necessity for complete dilatation of the cervix and more frequent use of episiotomy in primiparas has been noted, and with greater insistence upon these principles a lowered mortality should result. We believe that the greater number of fatalities in breech deliveries are the result of misguided haste in delivery, either before complete dilatation has occurred, or after the body has been delivered to the umbilicus. We are in complete agreement with Pierson's statement that "frantic haste as opposed to deliberate skill, has been the clinical error involved" in the treatment of breech deliveries.

CONCLUSIONS

1. The results are here reported of 550 consecutive breech deliveries at the Cleveland Maternity Hospital.
2. There were 400 full-term infants delivered, with a gross mortality of 8.5 per cent and a corrected mortality of 6.75 per cent.
3. The chief difficulty encountered was with undilated cervix. Manual dilatation of the cervix did not prove satisfactory; 23.5 per cent of the full-term deaths occurred where this procedure was adopted.
4. Breech labor in elderly primiparas is responsible for a high percentage of full-term deaths. The more frequent adoption of cesarean section in these cases is indicated where any possible disproportion exists or labor is unduly prolonged.
5. Breech labor and delivery in primiparas is considerably more dangerous than in multiparas.
6. The preservation of membranes has little effect upon the duration of labor, but it greatly decreases the dangers of delivery.
7. Episiotomy is indicated in all full-term breech presentations in primiparas.
8. Gentleness, deliberation, and careful manipulation are the essential features of breech extractions.
9. Breech extraction under deep anesthesia and full dilatation, offers a satisfactory method of delivery in breech presentations.
10. The more frequent adoption of external cephalic version is recommended as the best procedure to lower the fetal mortality in breech presentations.

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CARDIAC DISEASE IN PREGNANCY*

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IT HAS been shown in animals, as well as in the human being,^{1, 2} that the heart output increases during pregnancy. In normal gestation in women the cardiac output begins to rise above the normal level at the start of the fourth month and steadily increases, until at term it amounts to a value approximately 50 per cent above the normal. After delivery, the heart output slowly returns to normal, reaching its non-pregnant level within one month. Undoubtedly this marked increase in cardiac work is of the utmost importance in the consideration of heart disease as a complication of pregnancy. In the treatment of these patients we must give due recognition to this strain which labor still further increases. As yet, we have not evaluated the heart output during labor, but are tempted to believe that it will show a still further and substantial increase over the value at term.

A study of 81 pregnant patients, suffering from heart disease, and treated in the Woman's Clinic of the New York Hospital, forms the basis for this paper. These patients were seen during the first eight months following the opening of the Clinic on Sept. 1, 1932.

Incidence.—During the eight-month period, the total number of obstetric patients discharged from the Woman's Clinic was 1,951 and, of these, 81 suffered from heart disease. This represents an incidence of cardiac disease among our obstetric patients of 4.15 per cent. It is my impression that this is an incidence decidedly higher than that found in Baltimore or certain other sections of this country. An incidence of

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over 4 per cent of such a serious complication as heart disease places it in the foreground and so constitutes one of our most serious problems in obstetrics. The medical complications in pregnancy are usually regarded as of secondary importance, but the large number of women suffering from severe heart disease, as seen in our Clinic during this short period, has convinced me that more importance should be placed on this complication.

Treatment.—In order that cardiac patients may receive the very best care during their antenatal period, the Departments of Obstetrics and Medicine of the New York Hospital have cooperated to the extent that one morning each week is devoted to such patients, each of whom is seen by the resident physician and the obstetrician. We endeavor to have these patients come to the cardiac clinic in our antenatal department as early in pregnancy as possible. If the condition warrants it, the patient is admitted to the hospital for a complete study. Otherwise, she attends the cardiac clinic every week or two until it is felt that she should be admitted to the hospital. After admission this patient is again seen by the resident physician and obstetrician, and so the antenatal as well as the hospital study is conducted by the same persons. This leads to more uniform opinions and results. In addition to these two persons seeing all cardiac patients, we have a consultant cardiologist who sees these patients with the resident physician and the obstetrician at regular intervals. If necessary, a third internist is called in in consultation.

Most of our cardiac patients have been admitted to the hospital two months or longer before term and have been studied with the purpose of evaluating the cardiac reserve.

In the 81 pregnant cardiac patients we have had one death, an incidence of maternal mortality of 1.37 per cent.

CASE REPORT

The patient, a twenty-eight-year-old unregistered primipara, apparently five months pregnant, was admitted to the hospital on April 21, 1933. She was seen one hour prior to admission in the office of a senior member of the attending staff. At that time she was found to be dyspneic, cyanotic, and had severe coughing spells, raising a considerable amount of blood-stained sputum. It was obvious, following a hurried examination by the obstetrician, that the patient was five months pregnant and had marked cardiac failure, with a temperature of 35.8° C., pulse rate of 120, respirations 60 per minute, and a blood pressure of 70/30. Her respirations were labored, and she was forced to sit up straight in bed in order to breathe. No time was lost in placing the patient in an oxygen tent. The medical consultant was summoned at once. She was immediately given 7.5 gr. of caffeine sodium benzoate hypodermically, as well as morphine 16 mg. and atropine sulphate 0.4 mg. Two hundred and eighty cubic centimeters of blood were drawn from the right antecubital vein. The patient's pulse rate at this time was about 130 per minute, varying in volume and very irregular. Onabain $\frac{3}{8}$ mg. was then given intravenously. The pulse rate improved only slightly. Three minutes later she began to show increased cyanosis and promptly became unconscious. Many moist râles could be heard at

both bases and a bubbling sound throughout the entire chest. Cyanosis became more marked and the patient became very cold and livid. There was no attempt to make any pelvic or abdominal examination because of the extreme severity of the cardiac condition from the time of her admission at 10:30 A.M. In spite of all that could be done for the patient, she steadily grew worse, and at 1:00 P.M., or exactly two and one-half hours from the time of admission, she died.

This death is a direct result of negligence on the part of both the patient and her husband. It was learned that the patient had been told by her family physician three months before her admission to this clinic that she was suffering from a heart condition and should consult an obstetrician and a cardiologist. She not only refused to do this but failed to see her family physician again.

TABLE I. TREATMENT IN CARDIAC DISEASE IN PREGNANCY

Discharged before delivery (not yet delivered)		16
Discharged before delivery (delivered)		8
Abortions		
Completion of inevitable abortion	2	
Therapeutic, supravaginal hysterectomy	3	
	—	5
Premature delivery		
Spontaneous	5	
Operative, low cervical cesarean section, tubal sterilization	1	
	—	6
Full-term spontaneous delivery		24
Full-term operative delivery		
Low forceps	11	
Mid forceps	3	
Breech extraction	3	
Induction of labor, bougie	1	
Replacement of inverted uterus	1	
Classical cesarean section, tubal sterilization in 1 case	2	
	—	21
Died undelivered		1
		—
Total		81

The detailed methods of treatment in the cardiac patients is shown in Table I. A study of this table will show that 24 of the 81 patients had full-term spontaneous deliveries, while 21 had full-term operative deliveries. It is our practice, whenever indicated, to shorten or do away with the second stage of labor in patients suffering from cardiac disease, and this will account for the high incidence of forceps application. It will also be seen that in six patients the pregnancy was ended by cesarean section, an incidence of cesarean section of 7.4 per cent. The incidence of cesarean section throughout our clinic is about 3 per cent. The reason for this increase in incidence in cesarean section in cardiac patients is twofold: first, a cesarean section performed under proper open ether anesthesia, or perhaps local anesthesia, represents less of a strain to the heart than does a long and hard labor; and second, it is often advisable to sterilize the patient in order to prevent a subsequent pregnancy, and this can readily be done at the time.

It has been the custom in some clinics to divide the cardiac patients into groups such as Class 1, Class 2, and Class 3. We have attempted to

do this in certain of our patients, but we may say that, in general, such a grouping of patients is unsatisfactory and inaccurate. Each patient has to be studied individually. Where the patient has had no sign of decompensation, has gone through pregnancy quite comfortably, and approaches labor with a normal pulse and normal respiration, it is our rule to allow such patients to have spontaneous delivery. Should they show an increase in pulse during the first stage of labor, or any other sign of cardiac strain, it is our rule to shorten labor by the application of forceps as soon as the cervix is fully dilated. As will be seen from Table I, the majority of our patients fell into this category, either delivering spontaneously or delivering with forceps application.

Approximately one-fifth of our cardiac patients showed some sign of decompensation during pregnancy. Whenever a patient shows any sign of a break, she is immediately brought into the hospital and treated for her heart condition. It is our custom to have these patients in bed for at least two weeks before we decide as to the obstetric procedure to be followed in delivery. During these two weeks, one obtains a fairly accurate idea of the cardiac response to rest in bed and digitalis, and one is thus able to obtain some idea as to what the heart will do at the time of delivery. There are certain obstetric clinics in this country where digitalis is not administered to these patients. We, on the contrary, feel that wherever necessary the heart should be completely digitalized before labor sets in or any operative procedure is instituted. I can best illustrate the handling of such a patient by giving a short résumé of the treatment of such a patient.

A thirty-four-year-old para xii gave a history of eight full-term pregnancies and four miscarriages, and was admitted to one of our obstetric pavilions on Dec. 16, 1932, with a diagnosis of pregnancy of eight months' duration, complicated by cardiac disease. Her calculated date of confinement was Feb. 11, 1933. In her past history one gets a definite story of early rheumatic heart disease. In 1926, she was told that she had a "weak heart" and had to be cautious. In 1929, she was advised against further childbearing because of her cardiac condition. On admission to the pavilion she appeared uncomfortable, was dyspneic and orthopneic, and had a pallid skin. There were audible rhonchi in her chest, and numerous medium moist râles over both lung bases. The heart was found definitely enlarged with a diastolic thrill. On auscultation, a mumbling diastolic murmur was heard with an increased mitral first sound, also a systolic blow and increased second pulmonic sound. The consulting cardiologist saw the patient soon after admission, and it was his impression that she had a rheumatic heart disease, with mitral stenosis and insufficiency, early myocardial insufficiency with pulmonary congestion. She was given special treatment for her cardiac condition, including a complete course of digitalis, and followed very closely from day to day by the medical consultant. The patient responded satisfactorily and her condition showed marked improvement. On January 27, forty-two days after admission, it was thought that the patient was ready for operation. Under open ether anesthesia, a classical cesarean section with sterilization by tubal resection was performed. A normal, living, female infant, weighing 3,220 gm., was obtained. The patient stood the operation well. She had a smooth postoperative course and was discharged in good condition on the twenty-

second day following operation and the sixty-fourth day following her admission to the hospital. She was referred to the cardiac clinic for routine follow-up at regular intervals.

This patient represents one of 6 patients who were kept in the hospital for a period of a month or longer and then delivered by cesarean section under open ether anesthesia. It is our rule that, in a patient who has had a definite break in compensation of the heart, interruption of pregnancy with sterilization must be most seriously considered. In general, such patients should not be allowed to continue with their pregnancy, and they should certainly not have further pregnancies. Too often we make the error of allowing the patient to continue with the pregnancy in order to obtain a viable child, and sometimes even allowing her to go to term and through labor. I feel very strongly that a patient with a break in compensation should certainly not be allowed to go to term and through labor. A second break may prove fatal. As stated in the introduction of this paper, the cardiac output increases steadily from the fourth month of pregnancy until term. The longer the pregnancy proceeds the greater the strain on the heart. Labor adds a still further strain of unknown magnitude with the result that, if a break in compensation does not occur during pregnancy, it may readily occur during labor. I can again best illustrate my belief by citing the history of a patient who had an acute heart failure during labor. We expected this patient to die and can take no credit for the fact that she is today living.

A twenty-three-year-old primipara was registered on Oct. 4, 1932. On the initial examination it was learned that she had a cardiac lesion with a past history of broken compensation. Her calculated date of confinement was Nov. 27, 1932. On October 31, she was admitted to the delivery floor after having begun labor spontaneously at home six hours previously. On admission to the delivery floor, her pulse was 132 and her respirations 36 per minute. She was definitely cyanotic and dyspneic. The baby lay in R.O.A., the fetal heart was heard in R.L.Q. at the rate of 136 per minute, and the head was engaged. Rectal examination showed that the cervix was thin and about 4 cm. dilated, the head was engaged at a level just above the spines, and the membranes were intact. Very soon after admission, the patient became subject to coughing spells, and within four hours she was extremely short of breath, markedly cyanotic, and began to cough up blood; in short, her condition had suddenly changed for the worse. The medical consultants were immediately summoned. They found that the patient had pulmonary edema and cardiac decompensation. Prompt delivery of the patient was advised and emergency therapeutic measures were ordered for her cardiac condition. The patient was promptly delivered by low forceps since the presenting part was found on the perineum and the cervix fully dilated. A normal, living, female infant, weighing 2,800 gm. was extracted. The patient was given ouabain intravenously, receiving 4 c.c. (0.5 mg.) immediately after delivery, 2 c.c. (0.25 mg.) fifteen minutes later, and 2 c.c. (0.25 mg.) fifteen minutes after the second administration, a total of 1 mg. of ouabain in thirty minutes, intravenously. During delivery her pulse became imperceptible, and immediately after delivery she was placed in an oxygen tent. Her re-

sponse was satisfactory. She was followed very closely during the puerperium by the cardiologist. After a satisfactory convalescence, she was discharged on the twenty-sixth day following her delivery and referred to the cardiac clinic for follow-up. Her pulse is shown in Chart 1, from which it can be clearly seen that she had an acute cardiac break. The pulse and the respiration returned to normal approximately twenty-six days after delivery.

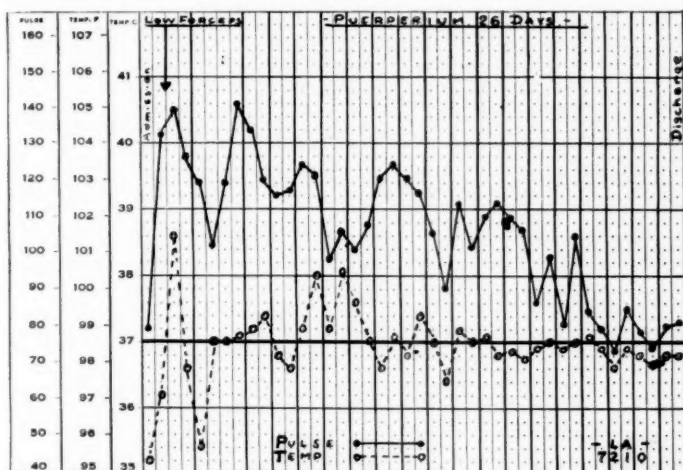


Chart 1.

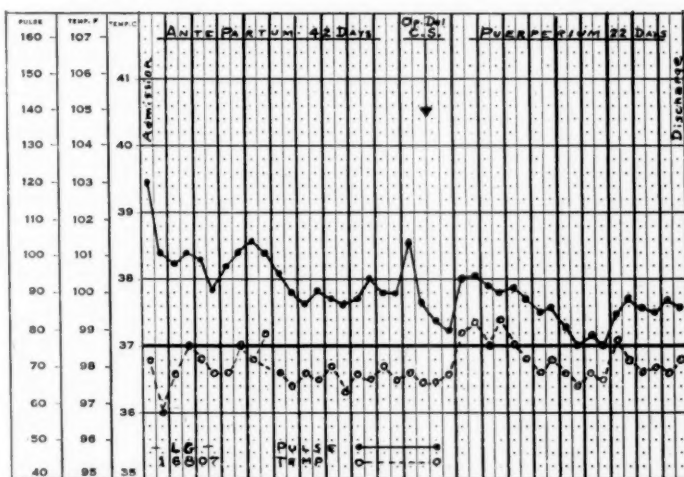


Chart 2.

The above history clearly indicates that this patient should not have been allowed to go to term and should certainly not have been permitted to go into labor. The procedure of choice in this patient would undoubtedly have been hospitalization after the very first sign of cardiac embarrassment, followed by operative interruption of the pregnancy as soon as the patient's condition had improved to an optimum with rest in bed, digitalis, and proper diet.

It must be clear to all that no rule can be laid down, that each case must be studied individually and carefully, and that should we allow patients with cardiac disease to go to term and through labor, we must feel reasonably sure that the heart can stand the increasing strain of pregnancy and of labor. Approximately only one-fourth of our cardiac patients were able to do this, the remaining 75 per cent having had

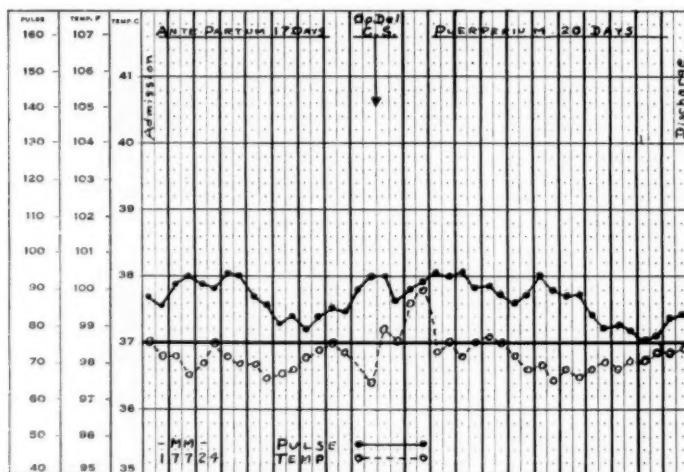


Chart 3.

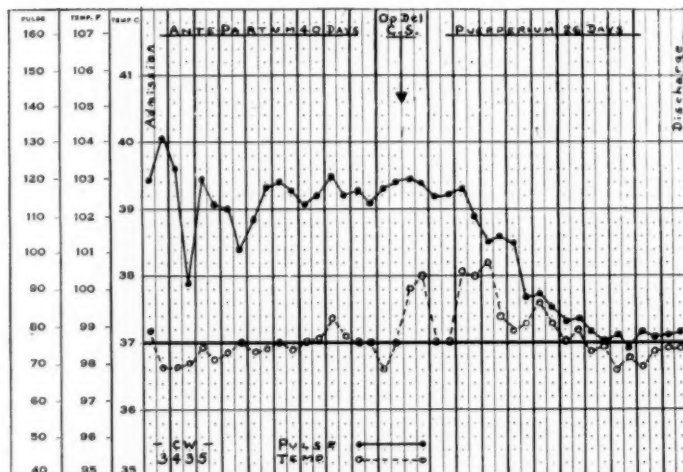


Chart 4.

some other type of operative delivery. The reason for such an operative delivery is to do away with or lessen the strain of labor.

The pulse and respiration are among our best indications as to the behavior of the heart while we have the patient under observation. In order to illustrate the value of the pulse, I have prepared charts on five patients during the antepartum and postpartum periods. The first

three of these (Charts 2, 3, and 4) show the pulse and respiration in three patients who were studied for a long period in the hospital, followed by cesarean section. It will be seen from these three charts that the operation had no effect on the pulse. The last of these three patients (Chart 4) illustrates clearly how the heart returned within a period of about three weeks to normal following cesarean section.

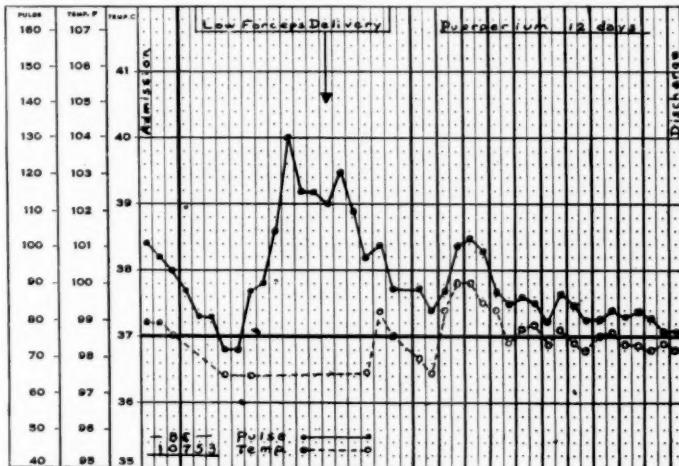


Chart 5.

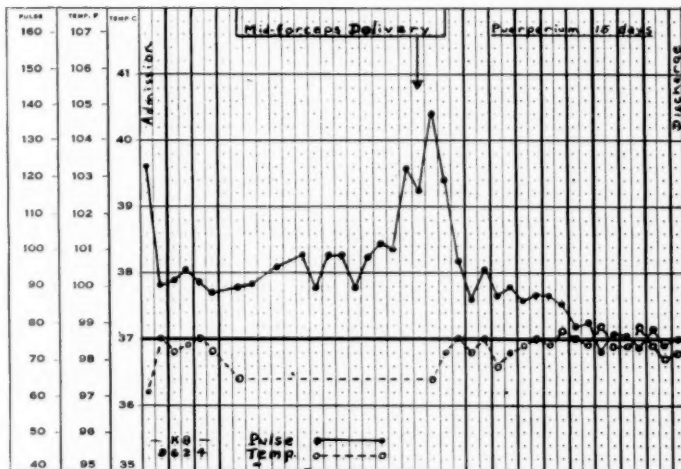


Chart 6.

The last two charts (Charts 5 and 6) represent the findings in two patients who were delivered by forceps. The pulse in each case rose almost perpendicularly during labor, in one instance as high as 140 per minute, in the other as high as 130. This strain of labor undoubtedly had a deleterious effect on the heart in each of these patients, and it was felt that labor should be shortened by the application of forceps in the

beginning of the second stage. Following delivery, the pulse and respirations slowly returned to normal, reaching the normal level approximately two weeks following delivery.

SUMMARY

In conclusion, we may state that pregnant patients suffering from heart disease may in general be divided into three groups, although these groups are not definite and often overlap one another. In Group I we may place those who have some history of heart disease, who show a heart lesion, either congenital or acquired, but who have not had any sign or symptom of cardiac decompensation and who are able to withstand the usual strain of everyday life without any signs of decompensation. These patients are able to climb stairs, one or two flights without undue dyspnea, they are not conscious of cardiac embarrassment, except, perhaps, on extreme muscular effort. In Group II we may place those patients who have a cardiac lesion, have no history of cardiac decompensation, but who are forced to limit their activities. A specific instance of such a patient would be a woman who is unable to climb a flight of stairs without resting at the completion of it and yet does not show any definite sign or symptom of a break in cardiac compensation. The patient in this class is conscious of the fact that her activities must be limited in order to live comfortably.

In Group III we place those patients who have a definite history of cardiac decompensation. These patients have been incapacitated at some time or other during their life because of that heart disease. The treatment in this class of patient should undoubtedly be radical. In general, a pregnancy should not be allowed to continue, and a subsequent pregnancy should be prevented by sterilization.

The treatment in the first class of patient usually consists in careful antenatal examinations and observation, admission to the hospital a week or two before term, with spontaneous delivery under ether anesthesia. The treatment in the second class of patient is an even closer vigilance, admission to the hospital a month or more before term is reached, and avoidance of the second stage of labor by forceps application on full dilatation of the cervix.

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525 EAST SIXTY-EIGHTH STREET

FETAL MORTALITY IN CONTRACTED PELVIS WITH PROLONGED LABOR AND DELIVERY THROUGH THE BIRTH CANAL

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THE decision as to the course to be pursued in the management of cases of so-called "borderline" contracted pelvis is a particularly difficult one. No clinical judgment is required to predict delivery through the birth canal in a woman whose pelvic measurements are normal and whose child is not excessive in size. Likewise, it is simple to elect cesarean section for a term pregnancy in a case of marked pelvic contraction. However, a decision as to elective section or trial of labor in a patient whose pelvis is slightly contracted, when the child does not seem overly large, and when disproportion is slight, calls for the nicest clinical judgment. In an effort to avoid unnecessary cesarean sections the custom has developed in doubtful cases of allowing the patient a "test of labor" which may terminate in normal delivery or delivery through the abdomen by the low cervical route. This test of labor has received many interpretations, varying from a certain number of hours of first stage pains to a duration of two hours in the second stage of labor. It was the definite feeling of the late Dr. Williams that in order for a test of labor to be significant, the patient should go through a two-hour second stage, with the membranes ruptured, and with the aid of her own expulsive efforts. Obviously, following this procedure, many women with slight degrees of pelvic contraction have been delivered spontaneously or by operative means through the birth canal, in whom a shorter test of labor would have terminated in cesarean section. It has been our impression for some time, however, that many of these women have had prolonged labors (over thirty hours) and that their delivery, other than by cesarean section, has been attended with a high fetal mortality. Accordingly, it seemed proper to investigate the outcome to the child in cases of prolonged labor, contracted pelvis, and delivery through the birth canal. The results of this investigation are presented in the following paragraphs.

A search through the records of all the patients delivered on the Obstetrical Service of the Johns Hopkins Hospital from its inception in 1896 to the end of 1931, revealed 422 cases satisfying the above-mentioned criteria. It should be stated that all pelves are classified as contracted when the diagonal conjugate measures 11.5 cm. or less, regardless of other measurements. This series does not include pelves with outlet contractions alone, but does include those cases with nar-

rowed intertuberos measurements where there was a concomitant shortening of the pelvic inlet. It should also be noted that the series includes only those patients delivered through the birth canal and omits those in whom delivery was effected by the abdominal route following a test of labor. Finally, it should be stated that the series includes no instances of multiple pregnancy and hence the mortality rates given are not colored by this abnormality.

There were, then, 442 pregnancies in women with contracted pelvis terminated at or near term by delivery through the birth canal following a labor of more than thirty hours. In 85 instances, the child was either born dead or succumbed during the first two weeks of life from various causes, giving a gross mortality of 19.23 per cent. Certain of these deaths, however, were in no way related to the labor or contracted pelvis, but were instances of death in utero prior to labor, syphilis, hemorrhagic disease, congenital malformation, etc. Omitting deaths due to these unrelated causes, a corrected mortality of 13.56 per cent was obtained. The actual cause of death in each instance when determinable, will be listed later.

TABLE I. FETAL MORTALITY (GROSS AND CORRECTED) ACCORDING TO COLOR AND PARITY

	TOTAL DELIVERIES	GROSS MOR- TALITY %	CORRECTED MORTALITY %	GENERAL CLINIC POPULATION GROSS MOR- TALITY %
White, para 0	70	14.25	10.45	
White, para X	29	17.24	17.24	
Black, para 0	246	15.85	12.29	
Black, para X	97	31.96	18.52	
Total, para 0	316	15.51	11.88	
Total, para X	126	28.57	18.18	
Total White	99	15.15	12.50	4.69
Total Black	343	20.41	13.88	6.96
Total Both Races	442	19.23	13.56	5.78

Table I indicates the mortality rates, gross and corrected, in terms of color and parity of the patient. That more deaths occurred among the blacks than the whites of the series was an expected finding and one that pertains to the clinic population as a whole. It seemed noteworthy that for both races higher rates obtained in multiparous than in primiparous women. These differences are probably largely explained by the fact that the average baby born to a multipara weighs several ounces more than that of a primipara (8 ounces in the white and 5 ounces in the black race). Such observations indicate the hazard of disregarding even minor degrees of pelvic contraction solely because the patient gives a history of previous normal deliveries. It should be particularly noted that the mortality rates given for the series are consistently about three times as great as those pertaining to the general clinic population. In other words, our experience indicates that the risk to the child is markedly increased in prolonged labor through a contracted pelvis.

The effect of the type of pelvic contraction on fetal mortality is shown in Table II. For this purpose, the cases in the series have been divided into the three main

TABLE II. FETAL MORTALITY (GROSS AND CORRECTED) ACCORDING TO TYPE OF PELVIC CONTRACTION

	TOTAL DELIVERIES	GROSS MORTALITY %	CORRECTED MORTALITY %
Flat	29	27.59	22.22
Generally contracted	248	16.13	10.73
Rhachitic	159	23.27	17.01
Other types	6	0.00	0.00

varieties of pelvic abnormality observed, namely, flat, generally contracted, and rhachitic. It will be noted that the greatest risk to the baby occurs with flat pelvis and the least in the generally contracted type. It will be shown subsequently that these mortality rates may be directly correlated with the average weight of the babies born through the three types of contracted pelvis.

TABLE III. INCIDENCE PER CENT OF TYPES OF DELIVERY

	TOTAL CASES	INCIDENCE PER CENT
Spontaneous	241	54.52
Forceps	132	29.86
Breech extraction	14	3.17
Version and extraction	25	5.66
Destructive operations	24	5.43
Other operations	6	1.36

Table III is inserted merely to indicate the type of delivery following the prolonged labor. Almost half of the total cases were terminated by operative means and in 24 instances, or about 5.5 per cent of the total, delivery could only be effected by craniotomy. It might be noted that spontaneous termination occurred more frequently in the black than in the white race despite the higher fetal mortality in the former group. Also, it is of interest that some form of operative delivery was necessary much oftener in the multiparas than in the primiparas of the series.

TABLE IV. FETAL MORTALITY (GROSS AND CORRECTED) SPONTANEOUS VS. OPERATIVE DELIVERY

	TOTAL DELIVERIES	GROSS MORTALITY %	CORRECTED MORTALITY %
Spontaneous	241	7.47	2.62
Operative	201	33.33	27.17
Forceps	132	19.70	17.19
Breech extraction	14	42.86	38.46
Version and extraction	25	36.00	27.27
Destructive operations	24	----	----
Other operations	6	33.33	33.33

From a study of Table IV, it seems evident that when spontaneous delivery follows prolonged labor in contracted pelvis the results to the child are quite satisfactory, and indeed, a corrected mortality of 2.62 per cent could be considered as good in a series of normal patients with labors of average duration. However, if the labor had to be terminated by operative means the fetal mortality rose to an appalling figure, with a corrected death rate of 27.17 per cent. Of the various operative maneuvers used forceps were attended with the fewest fetal deaths. The exceedingly high mortality risk to the child when breech extraction or version and extraction were employed serves as additional warning of the dangers attendant on these procedures when any degree of pelvic contraction exists.

It seems proper at this point to discuss briefly the 24 instances of craniotomy in the series. Eight of the cases fall into the group of so-called correctable deaths, the child having already succumbed prior to the admission of the patient to the hospital. In four of these cases the child had died at some time during the prolonged labor but no attempts at delivery had been made prior to admission. In three other instances fetal death had been due to attempted operative delivery in the patient's home by outside agencies, and in the other case the child was macerated and showed at autopsy evidences of congenital syphilis. However, there remain 16 babies delivered by craniotomy in whom the fetal heart was in good order at the time the mother was admitted to the hospital. Four of these succumbed in utero either late in the first stage or early in the second stage of labor, but before operative procedures could be effected. In a fifth case, prolapse of the cord occurred and pulsations had ceased before anything could be done. There remain, then, 11 cases where the child reached the second stage of labor in apparently good condition and where craniotomy was done subsequent to other operative attempts at delivery. Among this group are 7 instances of craniotomy following attempted high forceps, most of which occurred in the early days of the Clinic before the advent of the low cervical section. The remaining cases comprise three following attempted mid-forceps and one following an unsuccessful attempt at version.

TABLE V. MEAN WEIGHT OF BABY ACCORDING TO TYPE OF CONTRACTED PELVIS

	WHITE	BLACK
Flat	3,327.38 gm.	3,375.00 gm.
Generally contracted	3,163.46 gm.	3,070.06 gm.
Rhachitic	3,125.00 gm.	3,079.08 gm.
Total contracted pelvis	3,173.47 gm.	3,081.62 gm.
General clinic population	3,390.70 gm.	3,165.37 gm.

Table V indicates the mean weight of the child in the different types of contracted pelvis and presents a comparison with the weights obtaining for the general clinic population as a whole. The table is included since it would appear that the weight of the baby and fetal mortality are closely correlated in the different types of pelvis. Thus, babies born to women with flat pelvises are about average in size, and in this group is found the highest fetal mortality. However, with generally contracted and rhachitic pelvises, the colored infants were about 3 ounces smaller than the average for the race in general, while white infants were $7\frac{1}{2}$ to 9 ounces below the average weight.

TABLE VI. GROSS AND CORRECTED FETAL MORTALITY ACCORDING TO WEIGHT OF BABY

WEIGHT IN GRAMS	TOTAL CASES	GROSS MORTALITY %	CORRECTED MORTALITY %
-2,499	46	19.56	11.90
2,500-2,999	136	13.97	7.87
3,000-3,499	170	18.82	14.81
3,500-3,999	74	22.97	18.57
4,000-	12	33.33	20.00
Unknown	4	----	----

Table VI offers a comparison between fetal mortality and the weight of the child at birth. The mortality is high in babies weighing less than 2,500 gm. at birth, a fact most readily explained on the grounds that the diminutive size of the child renders it more susceptible to damage from the strains of labor. With this exception, there was found a progressive mortality rate with increasing birth weight which serves to emphasize the importance of careful estimation of the size of the fetus in any case of mild pelvic contraction.

TABLE VII. CAUSES OF FETAL DEATHS

Not correctable	56	Correctable	29
Asphyxia	28	Dead on admission	15
Intracranial injury	16	Syphilis	5
Prolapse of cord	5	Hemorrhagic disease	3
Broken neck	1	Malformation	1
Fracture of skull	1	Premature separation	1
Craniotomy, living child	1	Eclampsia	1
Unknown	4	Pneumonia	1
		Status lymphaticus	1
		Infection	1

Finally, the cause of death to the child is portrayed in Table VII. We believe that in 29 instances the outcome was not dependent on the contracted pelvis of the patient or the treatment she received, and hence, designated these deaths as correctable. However, there remain 56 cases of fetal death (13.56 corrected mortality per cent) in which it is reasonable to assume that protracted labor, contracted pelvis, and delivery through the birth canal were directly responsible for the fatal outcome; and this figure would seem to offer a true estimate of the risk involved in such cases. It might be stated that in addition to the 16 deaths listed as intra-cranial hemorrhage it seems probable that more careful study would have increased the number somewhat at the expense of the larger number clinically attributed to asphyxia.

DISCUSSION

Delivery through the birth canal following labors of more than thirty hours in 442 women with some degree of pelvic contraction occasioned a gross fetal mortality of 19.23 per cent and a corrected mortality of 13.56 per cent. These rates are about three times as great as those obtaining for the general clinic population on the Obstetrical Service of the Johns Hopkins Hospital. The mortality was greater among black than white women and was higher in the multiparous than in the primiparous division in the series. The highest death rate was found in cases of flat pelvis, was somewhat less with the rhachitic variety, and was lowest in the generally contracted group.

Almost half the labors were terminated by some sort of operative means and in 24 instances craniotomy had to be employed. The corrected fetal mortality when the labor was spontaneous was only 2.62 per cent, but when an operative procedure was necessary, the death rate even after correction rose to 27.17 per cent, and was higher with breech extraction and podalic version than following forceps delivery.

The mean weight of a child born to a woman with a simple flat pelvis was about that of the average clinic baby, while with rhachitic

and generally contracted pelves the figure was several ounces lower. The fetal mortality varied directly with the weight of the child at birth. Fifty-six or approximately two-thirds of the total deaths were directly attributable to accidents of labor or trauma attained at various forms of operative delivery.

It is by no means the intention of the authors to question the wisdom of allowing women with "borderline" contracted pelves a test of labor, since such a procedure will usually result in adequate uterine contractions and reasonably prompt dilatation of the cervix. Furthermore, the results to the fetus in such cases and when the entire labor is of less than thirty hours' duration are quite satisfactory, with a gross mortality of 7.19 per cent, a figure less than $1\frac{1}{2}$ per cent above the rate pertaining for the general clinic material. However, if the trial of labor is allowed to progress more than thirty hours, the fetal mortality rises to the appalling figure of 19.23 per cent (gross), and the wisdom of allowing the test to become prolonged seems extremely dubious.

From the foregoing analysis it is felt that the following generalization may be made with regard to cases of contracted pelvis. If the breech is presenting and external version cannot be accomplished, delivery through the birth canal is an extremely hazardous procedure unless the child is obviously small. With a vertex presentation the most careful examination is necessary to determine the presence or absence of cephalopelvic disproportion and a history of previous spontaneous births by no means ensures a similar outcome in any given case. The most difficult problem seems to be that of determining the duration of a test of labor once such a procedure has been decided upon. The finding of 442 instances of prolonged labor in women with some degree of pelvic contraction indicates that the condition is a relatively common one. We believe that for a test of labor to be completely significant, it must include two hours of second-stage pains aided by the expulsive efforts of the patient herself. Such a procedure, however, is hazardous to the baby and seems particularly so following prolonged labor. Therefore, it is our opinion that a test of labor should not be allowed to progress more than twenty-four hours, providing pains seem adequate, unless all signs point to its speedy and spontaneous termination. It would seem far preferable for the child at that time to perform a low cervical cesarean section.

Even if full dilatation of the cervix is accomplished within the above time period the problem is not clear as to the type of delivery to be chosen. The operation of version and extraction is attended with extreme danger to the child in the presence of any degree of pelvic contraction. Fortunately, the application of forceps to the floating or lightly engaged head is rapidly falling into desuetude. Even the operation of midforceps is attended with considerable danger to the child,

and unless the cranial bones, not the caput succedaneum, are at the level of the spines such an operation seems open to question.

It is realized that the above policy would result in an increased number of cesarean sections and fewer tests of labor terminating in delivery through the birth canal. Furthermore, it must be recognized that the operation, even though done by skilled hands and under favorable conditions, carries with it a definite risk to the mother and one which increases with the advance of labor. Statistical reports of series of low cervical cesarean section (the operation of choice following test of labor) would indicate a mortality risk of between 1 and 3 per cent grossly, and it seems fair to state that this type of operation properly done after a well-regulated test of labor should not result in a death rate of over $1\frac{1}{2}$ per cent from related causes.

On the other hand, in our series of 442 cases, there were 6 maternal deaths (1.36 per cent) and 4 of these were directly attributable to obstetric procedures involved, giving a corrected mortality rate of 0.91 per cent. Thus it would seem that prolonged labor, particularly if terminated by operative procedures from below, entails an appreciable risk to the mother, and although this risk is somewhat less than if cesarean section is employed, the increased number of live births resulting from the latter operation and contrasted with a fetal mortality rate of 19.23 per cent from the former would seem to counterbalance it considerably.

CONCLUSIONS

1. The gross fetal mortality attendant on delivery through the birth canal following prolonged labor in cases of contracted pelvis was 19.23 per cent in a series of 442 cases and even after correction for unrelated causes was 13.56 per cent.

2. An increased death rate was observed among the black women of the group and was definitely higher in the multiparous than in the primiparous portion of the series.

3. The highest mortality was seen in cases of flat pelvis, and the lowest in the generally contracted variety with the rachitic group falling between the two.

4. Almost half the labors had to be terminated by some sort of operative means, and there were 24 instances of craniotomy.

5. The mortality rate was satisfactory if spontaneous delivery occurred but with operative procedures was 27.17 per cent even after correction. Breech extraction and podalic version were extremely lethal to the child.

6. Children born to women with flat pelvis were about average in size but were several ounces below normal if the pelvis was generally contracted or rachitic. The fetal mortality varied directly with the size of the child.

7. The wisdom of allowing a test of labor to progress more than twenty-four hours, providing uterine contractions are adequate, is dubious unless all signs point to speedy and spontaneous termination. Low cervical cesarean section at that time becomes the procedure of choice for the child, although entailing probably some added risk to the mother.

THE EFFECT OF PREGNANCY UPON THE URETERS OF COMMON ANIMALS

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THE physiologic dilatation of the abdominal portion of the urinary tract during pregnancy is a well-recognized phenomenon in the human being.^{1, 6} The right side of the urinary system invariably undergoes a gestational enlargement 2 to 3 times its diameter in the non-pregnant, while the left side hypertrophies to a similar degree in only 70 to 80 per cent of pregnant women.

Investigation of this phenomenon by means of intravenous urography, using the rabbit as experimental animal, disclosed the fact that no changes were observable in its urinary tract during pregnancy (see Section I). This observation prompted a study of the ureters of other common animals with special reference to gross and microscopic changes during pregnancy.

Nothing was found in the literature dealing with such changes in the ureters of pregnant animals. However, Hofbauer³ studied them in 14 pregnant women from material obtained at autopsy. Consequently, the present study was undertaken in order to ascertain what changes, if any, occur in the ureters of pregnant animals. It deals with: (1) measurement of roentgenograms, obtained by intravenous urography, of the ureter of pregnant and nonpregnant rabbits; (2) measurement of the whole ureter and of its component parts in histologic sections of 8 different species of pregnant and nonpregnant animals, including the rabbit.

I. ROENTGENOGRAMS OF THE URETER OF PREGNANT AND NONPREGNANT RABBITS

Ten pregnancies, occurring in 9 rabbits, were investigated by means of intravenous urography. Skiodan was used as the contrast medium, and the technic of injection and exposure was identical with that developed by Mengert.⁵ Antepartum roentgenograms were made during the second half of pregnancy. A second set of roentgenograms of the same rabbit was made between three and sixty-five days after delivery. Ureteral diameters of identical points of the upper and middle thirds of

each ureter were measured directly from the films. The difference between the average ante- and postpartum diameters of each portion of each ureter of the 10 sets of roentgenograms is shown in Table I, plus representing a postpartum increase, and minus a postpartum decrease in diameter. It will be seen that the average diameter of the ureter in the pregnant rabbit was slightly larger than that of the nonpregnant, except in one instance. However, this increase is so slight that it cannot be considered significant.

II. HISTOLOGIC SECTIONS OF THE URETERS OF 8 SPECIES OF PREGNANT AND NONPREGNANT ANIMALS

Materials and Methods.—Forty-two animals, half of which were pregnant, were used. The series included the cow, hog, macacus monkey, dog, cat, rabbit, guinea pig, and rat.

TABLE I. DIFFERENCE IN AVERAGE DIAMETERS OF THE RABBIT URETER ANTE- AND POSTPARTUM, AS DETERMINED BY INTRAVENOUS UROGRAPHY*

URETERAL PORTION		AVERAGE DIAMETERS (MILLIMETERS)				DIFFERENCE (ALGEBRAIC)
		ANTEPARTUM		POSTPARTUM		
		NUMBER FILMS		NUMBER FILMS		
Right	Upper	10	1.34	9	1.30	0.04-
	Middle	5	1.08	4	0.93	0.15-
Left	Upper	10	1.29	10	1.28	0.01-
	Middle	6	1.00	5	1.02	0.02+

*The middle third of the rabbit ureter is difficult to visualize. Hence, whenever the number of films is less than 10, it is because it was impossible to measure diameters from the roentgenograms. No account has been taken of the enlargement due to spread of x-rays from the animal to the film as this distortion is constant in each case.

Minus represents a postpartum decrease in diameter, thus indicating that the average diameter of the ureter during pregnancy was larger than the average diameter of the postpartum ureter. Plus indicates a postpartum increase in diameter. Note: With the exception of the middle portion of the right ureter, the changes are insignificant. Even this ureteral segment only shows a decrease of 15 per cent in diameter.

The stage of pregnancy was determined by comparing the crown-rump length of the fetuses with tables furnished by Dr. M. A. Emerson² of the School of Veterinary Medicine. The majority of the pregnant animals were in the middle and last trimesters, though one each of the guinea pigs, cows, and hogs were in the first trimester.

Cow and hog ureters were collected from local slaughter houses. Monkey ureters were obtained through the courtesy of Dr. C. G. Hartman.*

The cow, dog, cat, rabbit, guinea pig, and rat were killed by a blow on the head and the hog by bleeding after the throat was cut. In the case of the laboratory animals, a blow on the head was used to obviate any possible action of anesthetic drugs on the ureters.

*The author is indebted to Dr. C. G. Hartman of the Carnegie Institution of Washington, Department of Embryology, Baltimore, for placing preserved monkey carcasses at his disposal. Four of the animals were macacus monkeys from the Carnegie Colony. The remaining monkey, *lasiohyga albigularis*, was obtained by Dr. Hartman from the Chicago Zoological Gardens, where it had died during labor just after having been delivered of twins. Pregnant monkeys, 78 and 117, were the subjects of the experiments by Ivy, Hartman and Koff¹ on "The Contractions of the Monkey Uterus at Term."

Susa fixation in situ was used within ten minutes of death of the animal on all tissues except those obtained from the monkeys, cows, hogs, 3 rabbits, and 1 dog. The monkey carcasses had been preserved in formalin. Tissues from the cow and hog, the 3 rabbits, and 1 dog were removed within a few minutes of death, and fixed immediately in Susa fluid.

With the exception of the cow, blocks were taken from the lower, middle and upper thirds of both ureters. Those from the lower third of the ureter were cut from a point just below the broad ligament. The middle portion of the ureter was chosen arbitrarily, and the upper portion was cut at a point opposite the lower pole of the kidney. No blocks were cut from the upper portions of the cow ureters because sufficient ureter was not removed by the butcher. All tissues were embedded in paraffin and stained with hematoxylin and eosin.

Measurements were made from tracings obtained by projecting images of the slides upon a paper screen. The magnification was determined by projecting the image of the lines of a blood counting chamber under identical conditions.

Diameters were measured directly from the tracings. If a section happened to be cut diagonally, the shortest diameter was measured. Areas of the ureteral sheath, circular muscle and the mucosa were measured on the tracings with a planimeter.

Individual epithelial cells and their nuclei were measured by means of a microscope scale in a microscope eyepiece. This scale was not calibrated as only relative measurements were desired.

RESULTS

a. *Ureteral Diameters.*—No gross variation was observed in the intact ureters of freshly killed animals. In the human being, however, hypertrophic changes incident to pregnancy are readily observable.

One section from each portion of both ureters of each animal was measured. Table II shows the average diameters of constituent portions of the ureters and also the grand average of all portions of both sides of the ureter, for pregnant and control animals. In addition, the average ureteral diameter per kilogram of body weight is tabulated for those animals for which the weights were available. It will be seen that it is always greater in the nonpregnant control, thus indicating that there is no dilatation of the ureter during pregnancy. Even if ureteral diameters are not expressed in units of body weight, the differences between the pregnant animals and the nonpregnant controls are not marked. It is surely not of the order of 2 or 3 to 1, which is the ratio usually found between the sizes of the ureters of pregnant and nonpregnant human beings.^{1, 6}

These findings indicate that there is no significant dilatation of the ureter during pregnancy in the animals studied.

b. *Relative Area of Ureteral Sheath.*—The areas of the sheaths of the juxtavesical portions of the ureters were measured and are expressed in Table III as percentage of sheath area to the area of the ureter exclusive of the sheath. The ureteral area represents actual tissue and does not include the area of the lumen. It will be seen that the per-

TABLE II. AVERAGE URETERAL DIAMETERS*

ANIMALS			AVERAGE URETERAL DIAMETERS—MILLIMETERS										AVERAGE ANIMAL WEIGHTS GRAMS	AVERAGE URETERAL DIAMETER PER KILO ANIMAL WT.	ANIMAL CONDI- TION
SPECIES	CONDI- TION	NUMBER	RIGHT			LEFT			GRAND AVERAGE						
			UPPER	MIDDLE	LOWER	UPPER	MIDDLE	LOWER							
Cow	P	3	—	6.4	4.9	—	4.0	5.6	5.2	—	—	P			
	N	3	—	4.3	5.3	—	4.1	5.0	4.7	—	—	N			
Hog	P	2	2.3	2.4	2.5	2.8	3.2	2.4	2.6	—	—	P			
	N	2	2.8	2.3	2.5	2.5	2.3	2.4	2.5	—	—	N			
Monkey	P	3	1.6	1.2	1.6	1.3	1.2	1.3	1.4	—	—	P			
	N	2	1.1	1.1	1.0	1.7	1.1	1.1	1.2	—	—	N			
Dog	P	1	1.7	1.6	1.7	1.5	1.4	1.5	1.6	15,500	0.10	P			
	N	1	1.0	0.9	0.9	1.1	1.1	0.9	1.0	6,300	0.16	N			
Rabbit	P	4	1.0	0.7	0.8	1.0	0.6	0.9	0.8	3,788	0.21	P			
	N	4	0.8	0.6	0.7	0.7	0.7	0.7	0.7	3,163	0.22	N			
Rat	P	2	0.3	0.2	0.3	0.3	0.3	0.3	0.3	233	1.29	P			
	N	3	0.3	0.3	0.3	0.3	0.3	0.2	0.3	136	2.21	N			
Guinea Pig	P	4	0.6	0.5	0.4	0.5	0.4	0.5	0.5	699	0.72	P			
	N	4	0.6	0.5	0.7	0.6	0.5	0.8	0.6	594	1.01	N			
Cat	P	2	0.6	0.4	0.5	0.7	0.5	0.4	0.5	3,025	0.17	P			
	N	2	0.7	0.7	0.6	0.8	0.6	0.7	0.7	2,945	0.24	N			

*Showing average diameters of the separate portions, and of all portions averaged together, of the ureters of pregnant and control animals. "P" denotes pregnant animals; "N" nonpregnant controls.

NOTE: (a) no significant differences appear in this table except in the case of the dog; (b) when ureteral diameters are expressed as a unit of body weight in 5 species, there is no increase during pregnancy.

centage of sheath area is greater during pregnancy in 5 of the species. However, it is felt that this difference is truly significant in only 2 of them, the monkey and the cow. The relative percentage is reversed in 3 species: rabbit, rat, and hog. Nonpregnant controls of these species appeared to have larger sheaths. From the foregoing data, it appears that the ureteral sheath seems to be an extremely variable quantity in these animals, and does not follow any set rule with regard to pregnancy.

TABLE III. PERCENTAGE OF URETERAL SHEATH*

ANIMAL	SECTIONS OF JUXTAVESICAL PORTIONS OF URETERS (NUMBER)		RELATION OF SHEATH AREA TO AREA INCLUDING CIRCULAR MUSCLE (PER CENT)	
	P	N	P	N
Monkey	5	4	73	38
Cow	3	5	77	49
Cat	4	4	48	38
Guinea pig	2	2	52	47
Dog	2	1	31	29
Hog	4	4	19	22
Rat	3	6	19	30
Rabbit	4	4	38	74

*Showing area of sheath of juxtavesical portion of ureters of 8 species of pregnant and control animals, expressed as percentage of ureteral area exclusive of sheath. The area of the lumen is not included in either case. "P" denotes pregnant animals; "N" nonpregnant controls. Note: There is no constant relation among the species between percentage of sheath and pregnancy.

c. *Area of Circular Musculature.*—Table IV shows the average area, in square millimeters, of the circular musculature of the juxtavesical portion of the ureter of the various pregnant and nonpregnant animals. It will be noted that only 3 species, monkey, hog, and dog, presented an increased area of circular musculature during pregnancy. Of these, the only difference which appears significant is shown in the dog. When it is remembered that the pregnant animal weighed twice as much as the control, the significance of this difference is materially diminished.

TABLE IV. AVERAGE AREA OF CIRCULAR MUSCULATURE*

ANIMAL	SECTIONS OF JUXTAVESICAL PORTIONS OF URETERS (NUMBER)		AVERAGE AREA OF MUSCULATURE (SQUARE MILLIMETERS)	
	P	N	P	N
Dog	2	1	0.72	0.29
Hog	4	4	3.12	2.73
Monkey	5	4	0.59	0.50
Cow	3	5	9.64	10.52
Cat	4	4	0.10	0.19
Rabbit	4	4	0.22	0.26
Guinea pig	2	2	0.16	0.18
Rat	3	6	0.02	0.03

*Showing average area of circular musculature of the juxtavesical portion of the ureters of 8 species of pregnant and control animals. "P" denotes pregnant animals; "N" nonpregnant controls. Note: The circular musculature is larger in the pregnant dog, hog, and monkey. However, the pregnant dog weighed nearly 2½ times as much as the control. If the two areas are expressed as units of body weight, they become: pregnant dog 0.05 sq. mm.; nonpregnant dog 0.05 sq. mm. The differences in areas shown for the monkey and hog do not appear to be significant.

In general, there appears to be no marked hypertrophy of the circular musculature of the juxtavesical portion of the ureter during pregnancy in the animals studied.

d. *Area of Mucosa*.—Table V shows the actual area of the mucosa of the various ureters in square millimeters. It will be seen that the average area of the ureteral mucosa of the pregnant animal was greater than that of the control in only 3 species: rabbit, monkey, and dog. Again, it should be remembered that the pregnant dog weighed twice as much as the control. Definite conclusions cannot be drawn, but the figures seem to show that there is no such change in the ureteral mucosa of pregnant animals as has been reported in the human being.³

TABLE V. AVERAGE AREA OF MUCOSA*

ANIMAL	SECTIONS OF JUXTAVESICAL PORTIONS OF URETERS (NUMBER)		AVERAGE AREA OF MUCOSA (SQUARE MILLIMETERS)	
	P	N	P	N
Dog	2	2	0.022	0.011
Monkey	6	4	0.034	0.017
Rabbit	8	8	0.034	0.017
Cow	6	6	0.091	0.133
Hog	4	4	0.071	0.082
Cat	4	4	0.038	0.058
Guinea pig	8	8	0.008	0.013
Rat	3	6	0.002	0.002

*Showing average area of mucosa of the juxtavesical portion of the ureters in 8 species of pregnant and control animals. "P" denotes pregnant animals; "N" non-pregnant controls. Note: The dog, monkey, and rabbit have an increased mucosa area during pregnancy. Again, expressing the areas for the dog as units of body weight, it is found that the area in the pregnant is 0.0014 and in the nonpregnant 0.0018 sq. mm.

e. *Size of Individual Epithelial Cell Elements*.—The mucosa of the juxtavesical portion of the ureter was studied further with respect to the size of individual cells and their nuclei, and to the number of cell layers. Five cells were measured in one section each of both ureters of 2 pregnant and 2 nonpregnant animals of each of 4 species, and the average number of cell layers in the mucosa counted. Table VI shows the results of these measurements. Actual size was not computed, each measurement being given only in terms of arbitrary divisions of the eyepiece scale. It will be noted that there was neither a significant increase in the size of individual cell elements or their nuclei, nor a significant increase in the number of cell layers of the mucosa during pregnancy in these animals.

f. *Histologic Analysis*.—All the slides used in this study were submitted for histologic analysis to Dr. George S. de Renyi of the Department of Anatomy, who found no constantly recurring differences between the ureters of pregnant and nonpregnant animals of any of the species.

The similarity of the juxtavesical portions of the ureters of a pregnant and of a nonpregnant macacus monkey is shown in Figs. 1 and 2. The first of these is a low power photomicrograph of the juxtavesical portion of the right ureter of a pregnant monkey, and Fig. 2 of the similar portion of the left ureter of a nonpregnant monkey.

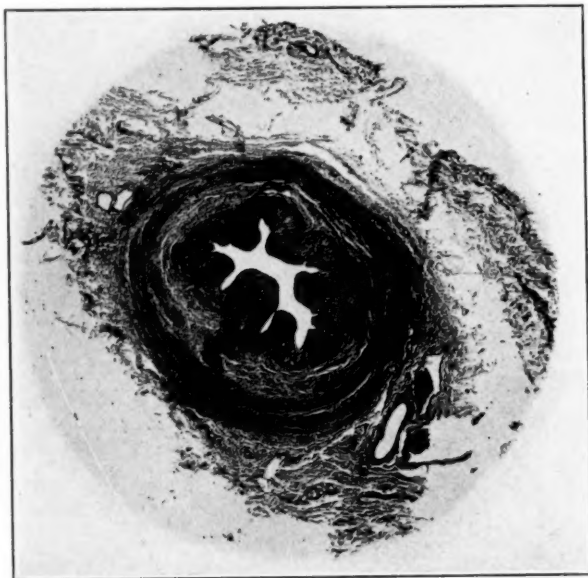


Fig. 1.—X44. Monkey 117, killed during labor. Section from the juxtavesical portion of right ureter. Compare with Fig. 2. Note: Absence of any characteristic peculiar to pregnancy.

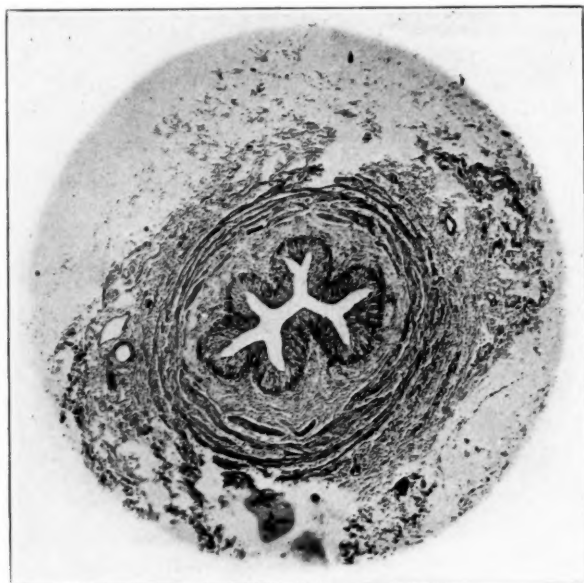


Fig. 2.—X44. Monkey 170; nonpregnant. Section from juxtavesical portion of left ureter. Compare with Fig. 1.

TABLE VI. RELATIVE SIZE OF CELL ELEMENTS, AND NUMBER OF CELL LAYERS IN MUCOSA*

ANIMAL	AVERAGE SIZE OF 20 CELLS (ARBITRARY MEASUREMENT)				CELL LAYERS	
	CELL		NUCLEUS		NUMBER	
	P	N	P	N	P	N
Cow	16.7	20.7	6.8	8.0	6	6
Monkey	15.9	16.7	9.6	10.4	6	5
Hog	16.8	17.6	9.2	9.4	5	5
Rabbit	17.2	19.7	8.8	8.5	6	6

*Showing relative size of epithelial cell elements and their nuclei, as well as number of cell layers in the juxtavesical portion of the ureters of 4 species of pregnant and control animals. Each figure of number of cell layers represents an average of the layers in 4 sections. "P" denotes pregnant animals; "N" nonpregnant controls. Note: There is no appreciable difference between the pregnant and nonpregnant animal.

COMMENT

It is recognized that the 10 rabbit pregnancies which yielded the data for Section I of the present paper are not a large number from which to draw conclusions. Nor are the 2 to 8 animals of each species enough to warrant conclusions with regard to that species. However, when all the evidence obtained by the two methods used and from each species of animals is so similar, and when it is considered as a whole, a few conclusions seem justifiable.

SUMMARY AND CONCLUSIONS

Urinary tract changes during 10 pregnancies in 9 rabbits were investigated by means of intravenous urography. Also, the ureters of 21 pregnant and 21 nonpregnant animals, representing 8 species including the rabbit, were submitted to a quantitative histologic study in order to determine if there were any gestational changes in diameter or in their microscopic structure. It was found:

1. That the ureters of the cow, hog, macacus monkey, dog, cat, rabbit, guinea pig, and rat do *not* dilate during pregnancy. This represents a true species difference between any of these animals and the human being.

2. A significant increase in the proportionate area of the ureteral sheath during pregnancy was noted in the monkey and the cow, and a significant decrease in the rabbit. It is felt that the ureteral sheath in the 8 species studied does not appear to follow any set rule with regard to pregnancy.

3. No significant hypertrophy during pregnancy was noted in the area of the circular musculature, or of the mucosa. The mucosa showed no increase in the number of cell layers or in the size of the individual cell elements.

4. From these observations it is concluded that pregnancy had no effect upon the ureters of the common animals studied.

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THE LESIONS OF FIFTEEN HUNDRED PLACENTAS CONSIDERED FROM A CLINICAL POINT OF VIEW

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OUR understanding of the pathologic lesions of the placenta is in an unsatisfactory state, both as regards their etiology and classification, as well as their clinical significance. The work of Eden, Williams, Dieckmann and McNalley, Siddall and Hartman in the English and American literature and that of Grosser and Hinselmann in the German have contributed the bulk of what we now know. However, they leave the reader with the impression that the subject is still vague from the pathologic and clinical points of view. This is particularly true of the latter. The meaning of the abnormal changes in the placenta to the obstetrician and his patients does not seem to have emerged from the efforts of these authors to catalogue and explain the lesion itself. That this fetal organ is the seat of a number of different forms of proliferations and degenerations, which alter its form and possibly its functions, has been proved. But the meaning of these, as far as the mother and her infant are concerned, is for the most part obscure. The inflammatory and syphilitic lesions are fairly well understood. The meaning of the hydropic degenerations, such as hydatidiform mole and minor vesicular changes in the villi, is to be included in the same category, due to the work of Essen-Moeller and Streeter. On the other hand, the commonest lesions of all, the obliterative changes, usually, though erroneously, known as "infarcts," and the cysts still remain an indefinite group. This may be due to the fact that the main effort has been spent in the direction of histologic studies. However, it seems to us important again to study these lesions from the combined histologic and clinical standpoint, but with the emphasis upon their clinical significance.

Our placentas are examined routinely in the gross. A careful description is made and they are weighed and measured. Following this, each placenta is cut into many parallel strips, one centimeter in

width, and the depths of the placenta carefully examined for lesions. Any abnormality is noted and those which seem to be of significance from the clinical point of view are given further study by histologic methods. In addition, microscopic preparations are made from the placentas of all syphilitic mothers and of those with premature or still-born fetuses. In this way, over 1,500 placentas have passed through our laboratories. Lesions of special interest have been worked up by means of differential staining methods as these were indicated.

Our study is based upon this material. In selecting and analyzing the lesions to be included, only those have been accepted which were of sufficient size, or if diffuse, of sufficient extent to have clinical significance. In the case of obliterative lesions (infarets) and cysts, we have accepted as our criterion a diameter of 2 cm. in the gross. This attitude is a point of departure from the work of our predecessors in this field. We realize that in taking it we are open to criticism because of our attempt to differentiate lesions that may have clinical importance from those having none. However, this is to be a practical study, in which, if it is to be of value to clinicians, such differentiation is of the utmost importance because the minor lesions occur with such frequency, in cases showing no other abnormality, that, unless discrimination is shown, the net result will be obscured in a mass of data that cannot be analyzed.

Our plan is to divide the study into four parts. First, we wish to make clear the incidence of lesions in the whole group of 1,500 placentas and compare our findings with those of other workers. Second, the incidence of the same lesions in normal mothers and infants will be considered. Then, with this as a background, the lesions occurring in a series of abnormal mothers and infants will be presented, and, finally, the findings in the placentas of all women with nonsyphilitic stillborn infants will be shown in an effort to indicate the significance of placental lesions in this group.

Table I reveals the incidence of the various lesions in the entire series of 1,500 placentas. The largest group is that called "obstructive and proliferative lesions." This is to be considered as embracing all types of "infarets." It is divided into two subgroups labelled "red" and "white," as these may have different etiologic significance. The red infarets have an incidence of 5.4 per cent and the white 13 per cent, together making a total of 18 per cent. In view of our method of selecting lesions, it will be important to indicate the findings of Williams who quotes 63 per cent for this group, Ravenstein 42 per cent, and Siddall and Hartman 67.7 per cent. These latter figures are undoubtedly correct from a pathologic point of view, but, since they include a majority of small lesions, we feel that our figure is a much more useful one and still includes all those abnormalities which could

TABLE I

WHOLE SERIES OF 1,500 PLACENTAS		NUMBER OF CASES	PER CENT OF WHOLE	
Obliterative and proliferative lesions ("infarets")	Red	82	5.4	18%
	White	200	13.0	
Premature separation of placenta		17	1.1	
Syphilis		17	1.1	
Cysts		18	1.1	
Hydatidiform mole		5	0.3	
Vesicular degeneration		10	0.6	
Chorionepithelioma		1		
Tumors		3	0.2	

have a definite influence either upon the infant or the mother. Tumors occurred three times and all were of the fibroangiomatous type. Their origin seemed to be undoubtedly from the chorion as all contained a high percentage of large, pale-staining chorion cells. None of the cysts were large and arose either in connection with the chorion plate of the fetal surface of the placenta or in the chorionic septa adjacent to the maternal surface. Syphilis was not a large factor in causing changes in the placenta. Indeed the figure of 1.1 per cent can be considered as a very low incidence. Vesicular degeneration occurred ten times. There were 5 hydatidiform moles with complete disappearance of the fetus. The other cases were instances which bear out the observations of Streeter, as they occurred in the placentas of women with normal infants, except as will be noted later in our classification of abortions and stillborn infants. Chorionepithelioma occurred once. Premature separation of the normally implanted placenta near term, with concealed or external hemorrhage, had an incidence of 1.1 per cent.

The occurrence of these lesions in the placentas of "normal" mothers and infants is shown in Table II. We exclude from this group all cases of syphilis, eclampsia or preeclampsia, nephritis, premature infants (weighing more than 1,500 and less than 2,500 gm.), and abortions (weighing less than 1,500 gm.). We do not exclude low reserve kidney as this group of cases does not show an incidence of placental lesions in any way different from the normal. The total number of this group of normal cases is 1,268. It is of interest to note that infarets, cysts, and tumors have the same incidence as in the total group, there being a slight difference only in the infaret group, where the occurrence is 3 per cent less than in the whole series. This we take as an indication that we have not been too radical in excluding lesions from our study that might have had serious importance for the mother. This has added significance when it is realized that at the time the lesions were segregated we had no knowledge as to the clinical history of the mother or infant.

In Table III, 232 pregnancies which were diagnosed as abnormal clinically, are analyzed. The outstanding features of this summary seem to be the relatively high incidence of infarction in eclampsia and preeclampsia, 40 per cent; syphilis 27 per cent; and premature

TABLE II

SERIES OF 1,268 "NORMAL CASES"		NUMBER OF CASES	PER CENT OF WHOLE	
Obliterative and proliferative lesions ("infarcts")	Red	52	4.0	15%
	White	141	11.0	
Cysts		3	0.2	
Tumors		3	0.2	
Hydatidiform mole		0	0	
Vesicular degeneration		0	0	
Retroplacental hemorrhage		0	0	

births 31 per cent. It is also notable that these lesions do not have as high an incidence in nephritis (14.5 per cent) as they do in the whole series of 1,500 cases. This would seem to be a contradiction to the results of other workers who find infarcts, especially of the "red" variety, more frequently in nephritis than in any other condition. We can offer one possible explanation. In our clinic, the incidence of chronic nephritis is relatively low, being only 3 per cent. This would of course reduce the number of lesions that might be regarded as associated with permanent kidney damage.

Another point of interest is the incidence of vesicular degeneration of the villi in 10 per cent of the placentas of premature births. This finding is in accordance with the work of Dr. Streeter, who has recently called attention to it.

As would be expected, retroplacental hemorrhage is frequent in abortions and in premature separation of the normally implanted placenta. In fact, it is so constant a finding that it might be considered as the normal mechanism for separation of the placenta from the uterine wall in the abortion group.

In view of the fact that this study is an attempt to point out the influence that placental lesions may have upon the welfare of the mother or the fetus, it is thought important to study the placentas associated with all nonsyphilitic stillborn infants. There were 38 such placentas (Table IV). Of these infants, 17 can be assumed to have died of extraplacental causes, such as prolapsed cord, multiple loops of cord about the neck, severe intrapartum infections, and hydrocephalus, an assumption which is borne out by the fact that no placental lesions were found excepting in the cases of intrapartum infection, and in these, although there was a definite infiltration of the tissues with the infective organisms, there was no definite reason for supposing that this was the cause of neonatal death.

TABLE III

SERIES OF 232 "ABNORMAL CASES"	54 ABORTIONS NONSYPHILITIC		79 PREMATURE BIRTHS		28 SYPHILITICS		17 ECLAMPTICS PREECLAMP.		54 NEPHRITICS		17 PREMATURE SEP. OF PLAC.	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Obliterative and proliferative lesions ("infarcts")	0	0	9	11	1	3	3	17	3	5.5	0	0
	3	5.5	16	20	7	24	4	23	5	9.0	1	5.5
Cysts	2	3.0	6	7	1	3	2	11	4	7.0	0	0
Hydatidiform mole	5	10.0	0	0	0	0	0	0	0	0	0	0
Vesicular degeneration of villi	1	1.5	8	10	1	3	0	0	0	0	0	0
Retroplacental hemorrhage	38	72.0	2	26	0	0	2	11	4	7.0	17	100.0

N.B. Incidence of infarcts in all "abnormal cases" is 18.1 per cent.

This leaves a group of 21 cases, diagnosed clinically as atelectasis, anomalies, and asphyxia. Seven of these cases showed no placental lesions of importance. The remaining fourteen, or 38 per cent of this group of 38 stillborns, showed marked infarction. These are outlined under the diagnosis of the mother. The severe toxemias, eclampsia, preeclampsia, and nephritis account for 42 per cent of the 14, and normal mothers account for the remaining 57 per cent. This would seem to indicate that in this small series, the maternal abnormality

TABLE IV

SERIES OF 38 NONSYPHILITIC STILLBORN INFANTS				
A. Cause of death probably extraplacental.	Prolapsed cord Cord about neck Intrapartum inf. Hydrocephalus	Clinical diagnosis	17 cases	No marked placental lesions
B. Cause of death doubtful	Atelectasis Anomalies Asphyxia	Clinical diagnosis	21 cases	*14 of this group had large placental lesions
*These 14 cases fall into the following Maternal Groups 38 per cent.				
1. Eclampsia and preeclampsia, 2 cases, both with large red "infarcts"				Toxemias
2. Nephritis, 4 cases, 2 with large red "infarcts", 2 with large white "infarcts"				42%
3. Normal mothers, 2 cases, both with large red "infarcts"	Premature infants, 6 cases all with large white "infarcts"			57%
	Full-term infants, 2 cases, both with large red "infarcts"			

may have had something to do with the occurrence of infarcts in the placenta, particularly as the placental lesions were of sufficient extent to suggest the possibility of their having contributed in part, at least, toward the infant's death before birth.

In summary it may be said that, in this study of 1,500 placentas, the chief abnormality found was some form of obliterative process which has been considered as having the same effect upon the placenta whatever its variety or origin. An attempt to associate these lesions with abnormalities in the mother has led to the conclusion that there seems to be no connection, as the incidence of placental lesions in the abnormal group was almost identical with those in the whole series of cases, the incidence in both being 18 per cent.

In the stillborn group there may be some connection between placental infarcts and severe toxemias, even though normal mothers who had marked infarction of their placentas had a higher incidence of stillbirths. However, Siddall and Hartman observed that mothers suffering from a toxemia of pregnancy, with large infarcts of the placenta, had infants with decreased birth weight, while the infants were

larger in such mothers without marked infarction of the placenta. This observation would seem additional evidence in support of our findings in the stillborn group.

The placenta must be regarded as an organ of such vast reserves that it can compensate for very great diminution of its function. It would seem clear that there are relatively few lesions that are of sufficient destructiveness to imperil the life of the fetus. Of these, syphilis, hydatidiform degeneration, premature separation, and faulty implantation are of greater importance than the so-called infarcts. Nevertheless, obliterative processes or infarcts, especially associated with a toxemia of pregnancy of severe grade, may and probably do have a deleterious effect on the infant.

In this study, there is no evidence, so far as we can judge, to support Dr. James Young who feels that obliterative lesions of the placenta are responsible, either wholly or in part, for the development of the toxemias of pregnancy. On the contrary, Kalima's contention that the severe toxemias, with hypertension and albuminuria, cause infarcts may have some basis, as we found that the incidence of large infarcts with damage to the infant was highest in this group.

111 EAST SIXTIETH STREET.

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THE CAUSE OF THE ONSET OF LABOR

A HORMONAL INVESTIGATION

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THE mechanism that deals with the onset of labor is a fascinating subject, and has interested those who have devoted themselves to the study of obstetrics from the very earliest times. It has always seemed to me another of life's unsolved mysteries that the pregnant uterus, which has been undergoing rhythmic contractions for many months, should suddenly change its whole state of being into powerful expulsive contractions which finally result in the delivery of the fetus. I am reminded of Sterne's able description of Mr. Shandy's amazement in his great anxiety over the proper delivery of his son Tristram, "that by force of the woman's efforts, which in strong labor pains was equal, upon the average, to the weight of 470 pounds avoirdupois, acting perpendicularly," the fetus was expelled.

The most important theories which have been advanced as to the causation of labor are: (1) the growing irritability, and increased distention of the uterus as gestation approaches termination; (2) the beginning dilatation of the lower uterine segment and cervix by the presenting part; (3) decidual changes in the nature of loosening, thinning out, and thrombosis of this layer; (4) gaseous changes in the placental blood, mainly increased CO_2 , and fetal metabolic products acting on the nervous centers of the medulla; (5) menstrual periodicity; it is generally accepted that the tenth menstrual date is the time for the termination of gestation; (6) the anaphylactic action of fetal blood, as evidenced by the incompatibility of the maternal and fetal blood groups; (7) senility of the placenta as manifested by infarcts in the maturing placenta; and (8) emotional causes, as fright, fear, etc.

A curious observation, which suggests that estrin may have a relation to the occurrence of parturition, is that in some animals, the guinea pig, the phenomena of estrus, absent during pregnancy, are seen immediately after parturition is completed and are then again absent until the termination of lactation. The occurrence suggests that at the time of parturition a sudden liberation of estrin takes place. That estrin plays some part in pregnancy is evident from the presence of large amounts in the urine toward the end of pregnancy and in the placenta.

Marshall suggested that one of the decisive factors in the onset of parturition was the reestablishment of the follicular phase of the ovarian cycle through the degeneration of the corpus luteum at the end of pregnancy. In cooperation with Dixon, he demonstrated that estrin and corpus luteum extracts act on an isolated uterus in no way differently from extracts of other tissues, which show definitely that the ovarian hormones have no direct influence in precipitating parturition, but that estrin causes an increase of pituitrin in the cerebrospinal fluid. They showed that the corpus luteum holds in abeyance the formation of a substance now thought to be estrin, which stimulates the posterior part of the pituitary gland. In late pregnancy the corpus luteum involutes, and when a certain point in its involution is reached, the stimulation of pituitrin secretion begins. These two observers have advanced an hypothesis that the onset of labor is due to estrin activity upon the posterior hypophysis, whose secretion, pituitrin, stimulates uterine contraction.

Maccchiiorulo's experimental investigations on the action of cerebrospinal fluid, withdrawn by lumbar puncture from normal, pregnant and parturient women, on the uterus of virgin, sexually immature and pregnant guinea pigs, confirm the results of the above experiments which show a scanty oxytocic activity of the lumbar fluid. Without completely excluding the presence of the hypophyseal hormone in the spinal fluid, it is possible to surmise that this hormone is not present in sufficient quantity to be demonstrable experimentally in all conditions. The excess of hormone encountered in the organism of pregnant women is not demonstrable in the results of the author's experiments, in which the various utilized fluids showed a practically identical action. Presumably, in pregnancy and in parturition, there coincides, simultaneously with the hypophyseal activity, an increase in the power of absorption of the hormone on the part of the blood vessels and a greater permeability of the meninges from within outward.

The theory of Marshall and Dixon has been modified by Parkes, working alone, and Bourne and Burn working together, who have observed the synergistic action of estrin and pituitrin on the isolated guinea pig uterus. Their contention is that the amount of secretion of pituitrin is constant, but that the uterine sensitivity to pituitrin varies. This sensitivity is increased if the uterus is first stimulated by estrin. The theory advanced by these observers is that estrin is held in abeyance by the presence of the luteinizing factors in the ovary, and as the maturity of gestation approaches, release of this inhibitory action of estrin is observed. The uterine sensitivity to pituitrin is then more marked and continues to be until the threshold is reached, when labor is precipitated. Brouha and Simmonet of France, and Knaus of Austria, have confirmed these findings.

According to Knaus' theory of the mechanism of labor, the uterine muscle is gradually increasing in size and power throughout pregnancy. During the first half of pregnancy, the uterine muscle is quite insensitive to stimulation, while in the later periods of pregnancy the sensitiveness of the muscle gradually increases and reaches a maximum at the time of labor. He has strong reason for supposing, therefore, that the decreased susceptibility is due to an action of the corpus luteum. According to this view, the initiation of parturition may depend not on an increased production of pituitrin, but on a sensitivity of the uterus greater than that hitherto found during pregnancy. The degeneration of the corpus luteum at the end of pregnancy, according to Knaus, brings about this result, and is, therefore, just as much the factor initiating parturition as is the hypothesis of Dixon and Marshall. Knaus looks upon the act of labor as the natural outcome of the change in the physiology of the uterine muscle, which occurs as pregnancy advances, and regards it as being entirely independent of any sudden influence brought to bear upon the uterus from outside.

In doing Aschheim-Zondek tests, Jeffcoate noticed an occasional unusual reaction. The animals' uteri were excessively dilated and distended with secretion, and the ovarian luteinization was less extensive than in the usual case. He concluded that the effect was due to the presence of a relative excess of estrin over Prolan B in the urine injected. The remarkable feature was that the patients whose urine gave the modified reaction almost invariably aborted, or passed a macerated fetus soon afterward. So intimate was the relation between the urinary findings and the subsequent clinical history of the patients that he was able to forecast, in several cases, that abortion was about to occur, or that the fetus was dead and the pregnancy likely to terminate. In confirmation of this supposition it was found that urine obtained from patients in the first stage of labor produced the same modified Aschheim-Zondek reaction. In view of these findings, and those noted during threatened abortions, it appears that estrin is intimately associated with uterine contractions.

In animal work on the isolated guinea pig uterus, Fontes, in France, has shown marked contractions of the uterus first bathed in a weak solution of estrin, and then stimulated by pituitrin. Similar results have been obtained by administering blood from a parturient woman. Postpartum blood, however, is negative to such stimulating uterine action. Fontes' conclusion is that there is an oxytocic factor present in pregnant blood which increases in potency or quantity as parturition approaches, and that this principle, when the necessary level required to precipitate labor is reached, is one of the main factors for the causation of labor. Also, serum from a woman in hard labor showed better results than that from one in moderate labor. From the fact that the oxytocic substance disappeared from the blood of his patients very shortly after delivery, Fontes concluded that this substance has its origin in the fetus.

Both Brdiczka and P. da Cunha have confirmed Fontes' observations. Clinical work based on this hypothesis has been done by Perez, who transfused whole, citrated blood, from 50 to 300 c.c., from parturient women into women past term. From 50 to 60 per cent of these women had labor successfully induced. This author likewise noted that blood taken from a woman in hard labor induced parturition more successfully than the same amount of blood withdrawn from a woman whose labor pains were neither forceful, nor frequent. From this it may be deduced that the precipitation of labor, and the degree of contractions, is the result of a quantitative oxytocic action.

In our own clinic, based on the animal work of Smith (M), and Kelly (L), who noted the induction of abortion from the administration of estrin, the estrin hormone in the form of theelin (Parke, Davis), was administered in varying dosages, singularly and daily to 10 pregnant women who were at term; only 3 delivered within thirty-six hours. The ovarian follicle fluid, aspirated at operation, was given to 2 women in similar condition; none delivered. This same hormone in the form of amniotin (E. R. Squibb & Sons), progynon (Schering & Co.), was administered alone, or in combination with pituitrin and pitocin (Parke, Davis), the active uterine stimulating principle of pituitrin, in various sized doses and at different intervals, to 30 full-term pregnant women. Seven delivered within thirty-six hours. Assuming that there might be an oxytocic factor present in the blood of parturient women, 25 c.c. of blood, taken from women in hard labor, were injected intramuscularly into the buttocks

of 3 women. One woman delivered in thirty-six hours. In no case was any maternal or fetal abnormality attributable to the injections. Table I denotes the findings.

TABLE I

	DELIVERED WITHIN 36 HOURS	FAILED
Theelin,* 1 to 4 c.c., singularly and daily	3	7
Theelin, 1 c.c. with Pituitrin, ℥ iv every 4 hr.	0	3
Aspirated follicle fluid, 1 to 4 c.c.	0	2
Amniotin, 1 to 3 pessaries, bid.	3	4
Amniotin, 1 pessary bid., with Pitocin, ℥ iv	0	1
Amniotin, 1 c.c. (hypo) with Pitocin, ℥ iv every 4 hr.	1	0
Amniotin, 1 c.c. (hypo) with Pituitrin, ℥ iv every 4 hr.	1	3
Amniotin (oral), 5 c.c. daily	0	3
Amniotin (oral, 5 c.c.) with Pitocin, ℥ iv bid.	1	2
Progynon, 1 c.c. with Pitocin, ℥ iv every 4 hr.	0	1
Progynon, 1 c.c. with Pituitrin, ℥ iv every 4 hr.	1	3
Parturient blood, 25 c.c. (hypo)	1	2
	11	34

*Theelin, 1 c.c. equals 50 rat units.

Amniotin, 1 pessary contains 40 Allen-Doisy units, one unit equal 4 mouse units.

Amniotin, 1 c.c. contains 20 Allen-Doisy units.

Progynon, 1 c.c. contains 25 Allen-Doisy units.

A possible upset of the theory of estrin stimulation of the uterus, resulting in increased sensitivity to pituitrin, as the causation of labor, seems to have appeared in the studies of Smith on the posterior hypophysis. This observer removed the posterior portion of the pituitary gland from 6 adult female rats. These animals were subsequently mated, and all bore litters. The course of pregnancy was normal and birth occurred at the usual time. From this evidence the conclusion may be drawn that in rats at least the secretion of the posterior hypophysis is unnecessary for either the onset or the maintenance of uterine contractions at parturition.

Allan and Wiles (unpublished and quoted by Gibbons) have shown that pregnancy may come to term in the ordinary way in an animal from whom the pituitary has been removed. It would appear, therefore, that neither the ovary nor the pituitary is necessary for the onset of normal labor.

COMMENT

The onset of labor occurs when the fetus has arrived at maturity, and is ready for external existence, much in the same manner as ripe fruit drops from the tree. The causation of the exact duration of labor is, as it always has been, most mysterious, and although not any more mysterious than many other wonders of nature, at least it is one which should be unravelled by continued research. Whatever be the cause of labor in ordinary circumstances, it must be due to some material circulating in the blood, and either must be very gradually increasing in amount for months, or suddenly poured into the blood stream.

The difficulty in inducing labor in certain cases is well known, while in others a gentle vaginal examination may start labor. All of us realize the vital necessity on some occasions of having to induce labor, and induce it quickly. I believe any method, whether it be medicinal, operative, or hormonal, must maintain a high efficiency, possibly 90 per cent success, if it is to be of value in the induction of labor. At the present time operative induction in the form of artificial rupture of the membranes, or introduction of a catheter or bag, is the most reliable for immediate precipitation of parturition. When the time element is not a necessary factor, medicinal induction, as described by the Watson technic, is of value, although success from this procedure varies widely, from 50 to 75 per cent. I believe that hormonal induction of labor will be of value when our knowledge concerning its regulation or mechanism is on a firmer basis. There is a remote possibility that it may even circumvent the disadvantages of the time element of medicinal induction, and the possible infectious incidence of the operative technic, since we know from our clinical experience that the onset of labor is not usually an insidious process, but an immediate precipitation.

The object in writing this paper is to show how profoundly ignorant we are of the causation of labor. Such ignorance should stimulate workers in the field of research in obstetrics to endeavor to place us beyond the realms of theory. If biochemistry could solve the cause of labor, we should probably have at hand some synthetic composition which would enable us to induce labor or premature labor when desired in the interest of mother or child.

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SOME ATTEMPTS TO INFLUENCE THE MENSTRUAL CYCLE IN THE MONKEY*†

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A LARGE series of facts has been accumulated in recent years to indicate that the female sex hormone (theelin, estrin, folliculin, amniotin) plays an important rôle in the physiology of menstruation. These facts may be summarized under several heads.

1. *Castration*.—It has long been known that double ovariectomy in women may be followed by bleeding. This is almost always the case if the operation is performed when one or the other ovary contains a large follicle or a corpus luteum, more rarely earlier in the cycle; it is, in fact, sufficient to remove the active ovary. The same is true of the monkey (Allen, van Wagenen and Aberle, etc.), in which castration brings about bleeding even if the ovaries do not contain large, visible follicles. Van Wagenen and Aberle¹ found that a second bleeding ensued after castration performed before the normal flow had ceased, say on day 4 or 5. It seems reasonable to presume that the bleeding is due to the withdrawal of female sex hormone with the ablation of the ovaries. If this explanation is correct, the withdrawal of minimal quantities is effective, for I have observed bleeding in adult monkeys after removal of ovaries apparently inactive and weighing only 140 mg.; likewise in one young monkey after she lost ovaries weighing less than 45 mg. each.

2. *Injection of Female Sex Hormone*.—Theelin or amniotin injected into preadolescent female monkeys or castrates is accompanied by microscopic bleeding and followed, several days (from four to nine) after cessation of the injections or reduction in dosage, by a more or less profuse bleeding, with destruction of endometrial tissue. The bleeding is usually of long duration (from ten to fifteen days). The light bleeding during the injections does not constitute menstruation but corresponds to proestrous or intermenstrual bleeding.

Here again, therefore, withdrawal of the hormone is followed by bleeding. In palpably sick or decrepit females, in nursing mothers whose uteri are normally hyperinvolved and, as will be noted later, in females running normal menstrual cycles, the female sex hormone is ineffective in moderately large doses (600 to 1,000 R. U. amniotin).

3. *Injection of Anterior Lobe Extracts*.—These always bring about bleeding in the intact rhesus monkey, young or old. Blood may issue

*Extracts from a paper read before the Boston Obstetrical Society, March 21, 1933.

†Thanks are due E. R. Squibb and Sons for the reagents used in these experiments.

from a tiny uterus no larger than a lead pencil. The effect of such injections is about the same as with female sex hormone but considerable bleeding may occur before the injections cease if these are long-continued. Is this bleeding a direct effect on the uterus or is it due to the stimulation of various follicles whose subsequent degeneration results in the "withdrawal" of the ovarian hormone?

If the effect is a direct one, injections into castrates should result in bleeding. This we attained several times. Thus, our preadolescent female (Monkey 114) which was castrated Feb. 16, 1932, received 63 c.c. of extract in fourteen days (March 14 to 27), bled considerably on the ninth and the tenth days of injection and lightly six days more. Two other castrates showed microscopic bleeding for several days during the injection, not afterward. Other investigators (Saiki) report negative results with castrates. It is probable, however, that menstrual bleeding with sloughing of endometrial tissue does not take place in castrates after anterior lobe administration.

The action of anterior lobe extracts in normal animals might be explained in terms of their stimulating the ovaries to secrete the female sex hormone. Saiki² was able to demonstrate some growth of ovarian follicles in his experimental animals that bled although the ovaries and uteri were not visibly enlarged. What is more significant, he was able to delay the onset of *experimental* (v.i.) bleeding for two weeks by following the anterior lobe administration with two weeks' injection of amniotin; no bleeding resulted until six to nine days after the latter was stopped. Therefore, it is argued, as long as there is a sufficient titer of female sex hormone, bleeding does not take place.

These facts, it is seen, fit in with the current gynecologic explanation of the cause of menstruation, namely, that this is due to the degeneration of the corpus luteum. The new aspect to this explanation lies in the emphasis on folliculin instead of the luteal secretion (progesterin), the human and the monkey corpora lutea being the only ones that secrete both hormones. Progesterin would, in this view, have nothing to do with the matter. This explanation is in line with the more indisputable observation that monkeys (and women?) may menstruate regularly without ovulating. I have several thousand such records; the Carnegie Colony has females that have menstruated without ovulating for several years, as I have learned by routine rectal palpations. Any theory of the cause of menstruation must take this phenomenon into account. The Allen-Corner theory, that the menstrual breakdown is due to the waning supply of female sex hormone, does this.

4. *Progesterin Injections.*—A discordant experiment, however, is that of Smith and Engle.³ Anterior lobe hormone was injected into a young monkey for twelve days, theelin the last four days of this period; finally the animal was castrated on the last day of the injections. There were

three reasons, therefore, why the animal should have bled four to nine days later. Beginning with the day following the operation progestin, a purely luteal extract free of female sex hormone, was injected for twenty-eight days, and bleeding was prevented for this period and six additional days. It is clear, then, that progestin must fit into the theory of the menstrual cycle in some way.

5. *Hypophysectomy and the Female Sex Hormone*.—Hartman, Firor and Geiling⁴ reported that in the hypophysectomized animal amniotin injections do not result in bleeding as previously described. They believed, therefore, that the female sex hormone acts through the hypophysis. Of the four animals hypophysectomized one bled after injections and clearly retained active anterior lobe tissue, since she was not insulin-sensitive. The three others failed to bleed after 310, 430, and 495 R. U. of amniotin, respectively, in the first tests made within a month after hypophysectomy. In two of these cases tests were run two and five months later and bleeding did follow the injection of 410 and 720 R. U., respectively, of amniotin, even though both animals were at the time still highly sensitive to insulin. One of these (Monkey 125), a young animal, has since passed many nonovulatory cycles; the other (Monkey 36), a multipara, after a year and a half of irregular, mostly non-ovulatory cycles, conceived, carried a baby to term, and suckled it. It will be interesting eventually to bring these animals to autopsy to study the restoration of a damaged hypophysis to a point adequate for reproduction.

6. *Is Prolan (Follutein Squibb, Antuitrin-S, the Anterior Lobe-like Substance of Human Urine of Pregnancy) Effective in Causing Uterine Bleeding?*—I have found that a slight bleeding may accompany the injection of Squibb's follutein. The bleeding may stop before the injections are discontinued. Engle⁵ found the same thing but only in normal females, not in castrates. However, I twice noted a slight bleeding in castrates, as the following protocol indicates:

Monkey 20, castrated a year previously, received 620 R. U. of follutein in gradually increasing dosage from Dec. 15 to 26, 1932. On December 18, 19, and 20, there was microscopic bleeding. A similar animal received 930 R. U. of follutein and 12 c.c. of growth hormone (Squibb) at the same time and showed red blood cells in the vaginal lavage on December 21 and 22, none afterward.

With Engle's suggestion that this effect of urine concentrate is non-specific and that the bleeding is not menstrual, I am in agreement, since the bleeding usually proceeds from an intact endometrium. A similar bleeding can, moreover, be brought about by liver extract. I have twice also seen bleeding following liver extract injections in females castrated a whole year before. This effect is probably not due to the small amount of female sex hormone which Morrell, et al., have found present in liver tissue.

The gonadotropic action of prolan (e.g. follutein Squibb) even when administered along with growth hormone (Squibb) is certainly minimal. Thus an adolescent female (Monkey 244) received between Jan. 27 and Feb. 15, 1933, 40 c.e. of growth hormone containing 5,073 R. U. of follutein. The ovaries did not enlarge, the uterus remained infantile (7 mm.), there was no bleeding—in short, the effect was zero.

7. *Can Follutein (With or Without Growth Hormone) Change the Menstrual Cycle?*—The following experiments were made in this connection:

Monkey 186.—Menstruation Sept. 21 and Nov. 7, 1932; interval forty-seven days. Nov. 15 to 28, 720 R. U. of follutein; on Nov. 28, 400 R. U. intravenously in one dose. Bleeding December 1 to 6. *Interval since last bleeding twenty-four days.* Did the injections bring on this bleeding? January 27 to February 17, 45.5 c.e. growth hormone and 5,710 R. U. follutein. No bleeding during injections, but vaginal desquamation greatly increased (evidence of ovarian activity), uterus enlarged from 14 to 16 mm., left ovary cystic at end of injections. February 23 a six-day bleeding began; vaginal desquamation low, as at the end of a normal cycle; ovarian cyst receded. *Interval since last bleeding eighty-four days.* Injections were resumed immediately: March 1 to 7, 25.5 c.e. growth hormone and 3,192 R. U. follutein were injected. Bleeding began on March 14. *Interval was this time reduced to nineteen days.* The right ovary became cystic during this interval, but this was clearly not due to the extracts, as the ovary was already large when the last series of injections began.

On March 2 the uterus was much enlarged (18 mm.). When the bleeding began on March 14 the ovary was reduced in size, vaginal desquamation was low (10 per cent), the uterus much smaller (14 mm.). The monkey bled spontaneously on April 10 *after an interval of twenty-seven days.*

Thus in this series of experiments three bleedings in succession were preceded by injections of prolan. Once a forty-seven day cycle was followed by an experimental one of twenty-four days and once a nineteen day cycle seemed induced after an unusually prolonged one. Three such bleedings so well timed with reference to injections would hardly be interpreted as spontaneous and without causal relation to them. Nevertheless the records of our monkey colony include just such bizarre behavior in the absence of treatment of any kind.

Two other animals behaved in a manner that left the observer in doubt as to whether the injections influenced the cycle or not. Finally two adult monkeys that were menstruating regularly (though entirely without ovulating) were clearly uninfluenced by the injections:

Monkey 180.—Bleedings: October 5, October 28, November 23, December 21; intervals: twenty-three, twenty-six, twenty-eight days. January 5 to 26, 1,512.5 R. U. of follutein injected. Bleeding was expected at the latest January 18 and it actually began January 19 (interval twenty-nine days). The next spontaneous cycle was thirty-three days in length.

Monkey 188.—Bleedings: October 12, November 7, December 2, December 27; intervals: twenty-six, twenty-five, twenty-five days. Injected exactly like Monkey 180. Bleeding was expected and actually occurred January 21 (interval twenty-five days), with a more profuse bleeding January 24. The next spontaneous bleeding occurred February 20 (interval thirty days).

It is apparent that in the last two cases menstruation came about on schedule time and the extracts were without effect.

8. *Can Female Sex Hormone in Reasonable Doses Influence the Normal Cycle?*—Since follutein has little effect so far as the causation of bleeding is concerned and hence may not be expected to influence the cycle, this does not hold for the female sex hormone whose action has been amply demonstrated. Two typical experiments may be cited:

Monkey 185 had been amenorrhoeic for months. January 5 to 10, 640 R. U. amniotin Squibb were injected. Bleeding began on the last day of injection and continued for fourteen days, but on January 13 and 18 no blood was found. On January 19 she bled more freely than before. This exacerbation in bleeding may have been the effect of the injections, the first bleeding the normal menstruation. But this is speculation.

Another case is more instructive:

Monkey 217.—Bleedings after nonovulatory cycles Oct. 5, Oct. 31, Nov. 25, Dec. 19, 1932, the menstrual intervals being twenty-six, twenty-five, and twenty-four days. January 5 to 13, 995 R. U. amniotin Squibb were injected. Bleeding occurred on the day expected, January 12, after a twenty-four-day interval and before the injections ceased. There was no further bleeding. The next spontaneous bleeding occurred February 13 after a thirty-two-day interval.

It appears, therefore, that once the menstrual cycle is in full swing, the rhythm is hard to upset, for the cycle in which the female sex hormone is administered is of normal length; the cycle of endocrine influences continues to run its course. The next following cycle was, however, almost uniformly lengthened, as though the administration of the hormone caused a temporary injury.

SUMMARY

The ovary and the anterior hypophysis are intimately involved in the control of the menstrual cycle and in the bleeding phenomenon itself. The female sex hormone looms large in the picture, but its exact rôle is not known. The anterior hypophysis is probably necessary for the theelin action in relation to bleeding.

Prolan, the concentrate of pregnancy urine; may cause a slight bleeding, like intermenstrual bleeding, from a grossly intact endometrium. But this prolan action is nonspecific, like liver extract for example, which also brings about bleeding. Prolan, in the form of follutein Squibb, potent for stimulation of the ovaries of rats, as is well known, and even more so of the ovaries of the opossum, as I have recently found, is hardly at all gonotropic in the monkey.

The course of the menstrual rhythm is, therefore, not influenced by follutein injections. Neither is it influenced by female sex hormone (amniotin Squibb), very potent in the causation of bleeding in castrates and young female monkeys. Large, though not excessive doses of amniotin are incapable of breaking in on the menstrual cycle, once this gets going.

Of interest to the clinician are two facts that appear from the preceding: (1) Reasonable doses of the biologic reagents here employed, while they cause more or less bleeding, bring about no grossly recognizable growth of the ovaries or uterus. The value to the female organism of this slight or even profuse single bleeding would seem to be most questionable; (2) but even these small doses apparently effect a slight injury, if one is so to interpret the slowing up of the cycle following the experimental injections.

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DISCUSSION

DR. G. VAN S. SMITH.—In pharmacology we were taught that it is much more difficult to upset a normal function with a reagent than to bring an upset function back to normal with the same reagent. The substance of this paper, I think, confirms it.

Our (Dr. John Rock, Dr. O. Watkins Smith, and the speaker) comparatively small experience clinically with estrin and prolan is practically similar to Dr. Hartman's.

During the past two years we have performed what we call our "ovulation test" on a number of patients (Smith, G. V., and Smith, O. W.: *Am. J. Physiol.* **100**: 553, 1932). In this test the cyclic presence of an active corpus luteum (presumably indicating recent ovulation) is shown by a peak in the urinary excretion of ingested estrin. Most of the patients upon whom the test was performed complained either of sterility, amenorrhea, or oligomenorrhea, but we have records of 9 patients with regular cycles who received from 200 to 600 R.U. of estrin daily (Schering Corporation "progynon") for from twenty-five days to four months. There occurred no discernible effect upon the rhythm of menstruation. Three patients upon whom the test was run for two months or more stated that their periods were somewhat more scanty than usual.

In connection with the possible influence of prolan on cycles, we recently gave fairly large amounts of follutein (Squibb) to a group of rats whose cycles had either ceased or become very irregular. In a large proportion normal cycles became reestablished within three weeks. Last summer we reviewed the records of 56 patients who had been treated with antuitrin-S (Parke, Davis and Company) for uterine bleeding of dysfunctional origin. Twenty-four were cases of menorrhagia, i.e., normal rhythm with excessive flowing. In 3 instances menstruation came five days late following treatment. Thirty-two were cases of metrorrhagia. With 4 exceptions, most of these patients tended toward a reestablishment of normal cycles following treatment. The 4 exceptions had from four to five months of amenorrhea. Thus prolan seems to have little effect on normal rhythm. In cases of upset rhythm, e.g., patients with metrorrhagia, prolan has more effect, as indicated by a return of normal cycles and in 4 instances by amenorrhea.

In treating these cases of dysfunctional uterine bleeding with prolan we have been especially interested in the findings when Aschheim-Zondek tests are performed. To date this test has been run on 66 specimens of urine and 9 specimens of blood from 30 patients. The specimens from 26 of these 30 patients *before*

treatment were positive for the so-called prolan A effect (open vagina, enlarged uterus, follicle ripening in the ovaries). Three of the four specimens that gave negative tests were from patients with intermittent staining. In 19 instances we were able to do Aschheim-Zondek tests both before and after treatment with antuitrin-S or follutein. The tests were all positive for the prolan A effect before treatment. Treatment was not followed by cessation of flowing in 2 cases and in these the prolan A effect persisted. Flowing ceased after a variable number of injections in the other 17 and in all but four of these the cessation of flowing was accompanied by a total disappearance of the prolan A effect. It seems paradoxical that the administration of prolan should cause prolan to disappear, but I believe the following explanation may be correct. The prolan A effect with the blood and urine specimens of these patients is almost certainly due to a substance from the hypophysis. The prolan extracted from the urine of pregnant women and named antuitrin-S or follutein may contain something from the hypophysis, but almost surely contains another factor, probably of placental origin, which favors luteinization. We are inclined to believe that this placental prolan either inhibits the hypophyseal prolan that gives the A effect or converts it into a factor that favors luteinization and cessation of uterine bleeding.

THE EFFECT OF JAUNDICE ON THE VAGINAL SMEAR PICTURE AND PREGNANCY OF THE RAT*

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THERE appears to be no work recorded in the literature appertaining to the effect of jaundice on the vaginal smear picture and pregnancy in animals. Many questions such as the following are unanswered. Can a normal pregnancy take place in a jaundiced animal? What is the effect of jaundice on the vaginal smear picture? Will jaundiced animals breed? Does the condition of icterus in a pregnant animal have any effect on the young? Are the fetuses also jaundiced? These questions have been considered in the following experiments.

Experimental.—Normal, adult female rats of tested fertility were jaundiced by ligating and sectioning the common bile duct either before breeding or at various stages during the pregnancy. All animals were mated with males of tested fertility. The animals were kept in individual cages on the following diet: ground wheat 72.5, fish meal 12.5, whole milk powder 12.5, alfalfa meal 2.5, sodium chloride 0.5, and calcium carbonate 0.5 parts.

The animals were divided into three groups. The members of Group I were jaundiced before breeding, those of Group II were jaundiced at various stages during pregnancy. The members of Group III were operated on without inducing jaundice. This last group was used to rule out the effects of the operation. Daily vaginal smear examination including a search for residual spermatozoa, increase in body weight, erythrocyte sign, as well as autopsy examination, was used to determine pregnancy.

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TABLE I. THE EFFECTS OF JAUNDICE ON REPRODUCTION IN THE ADULT RAT
Group I. Animals Operated on Before Breeding

RAT NO.	LENGTH OF LIFE (DAYS)	CAUSE OF DEATH	SIGNS OF PREGNANCY	REMARKS
7	21	Liver and kidney damaged	None	Vaginal smear normal
1009	56	Liver and kidney damaged	None	Vaginal smear normal
1008	90	Killed	None	Vaginal smear normal
9	32	Liver and kidney damaged to great extent	Artificial fertilization failed	Jaundice cleared up after 35-40 days
10b	37	Liver and kidney damaged	Artificial fertilization failed	
11w	40	Bile duct very large	Artificial fertilization failed	
		Ruptured bile duct	Artificial fertilization failed	
12b	80	Killed	None	Vaginal smear normal
14b	57	Killed	Artificial fertilization failed	Jaundice cleared up after 30 days
15w	32	Liver and kidney damaged	Artificial fertilization failed	Vaginal smear normal
8	21	Liver and kidney damaged	Artificial fertilization failed	Bile duct filled entire body cavity
		Pregnant	Artificial fertilization failed	Vaginal smear normal
38w	38	Liver and kidney damaged	Autopsy showed 5-day-old embryo	Liver almost white
			Artificial fertilization succeeded	
39p	41	Liver and kidney damaged	None	Vaginal smear normal
			Artificial fertilization failed	
61	56	Liver and kidney damaged	None	Vaginal smear normal
42	26	Bile duct ruptured	Artificial fertilization failed	Bile duct filled entire body cavity
34	19	Liver and kidney damaged	Artificial fertilization failed	Vaginal smear normal
41	33	Liver and kidney damaged	None	Vaginal smear normal
46	29	Liver and kidney damaged	None	Vaginal smear normal
		Ruptured bile duct	Artificial fertilization failed	
73	38	Liver and kidney damaged	None	Vaginal smear normal
64	26	Liver and kidney damaged	None	Vaginal smear normal
40	31	Liver and kidney damaged	None	Vaginal smear normal

TABLE II. THE EFFECTS OF JAUNDICE ON THE REPRODUCTION OF THE ADULT RAT
Group II. Animals Operated on at Various Stages of Pregnancy

RAT NO.	LENGTH OF LIFE (DAYS)	STAGE OF PREGNANCY AT WHICH OPERATED (DAYS)	OUTCOME	REMARKS	CAUSE OF DEATH
28P	10	1	Mother died	No sign of pregnancy at death	Ruptured bile duct
27P	26	1	Killed	Embryo 16 days old	Discrepancy in days unexplained
36P	14	2	Killed	Resorption	
33P	17	2	Killed	Resorption	
22P	54	3-4	Killed	No sign of pregnancy	
21P	11	4-5	Ruptured bile duct. No sign of pregnancy at death		Ruptured bile duct
24P	38	7-8	Pregnancy failed		
35P	6	7-8	Mother died	5 embryos 14-15 days old	Ruptured bile duct
19P	4	10	Mother died	7 embryos 12-14 days old	Liver damaged and a touch of lung involvement
18P	24	11	Six young born alive	Young underweight	Mother badly emaciated. Young raised and weaned at 25 days of age
16P	30	11	Five young born alive	Young small. Mother failed to care for them	Young died during first 24 hours.
26P	29	12	Three young born and reared	Young small	Lactation failed. Young weaned at 25 days. Appear normal
25P	8	12	Mother died	No sign of pregnancy	Operation successful. Liver and kidney damage marked
37P	8	14	Six young born alive	Failed to care for young	Mother and young died two days later
32P	16	13-14	Resorption		
31P	16	15	Eight young born, underweight	Young died two days later	Mother lost weight steadily and then died 10 days after delivery
30P	14	15	Six young born, underweight	Mother never cared for young	Mother died one week after delivery
29P	79	15	Six young born. Died first day	Young small. Appear normal	Killed. Nature reestablished duct, after which the animal went through a normal pregnancy
20P	3	16	Six normal embryos found at the time of the mother's death	Embryos about 20 days old	Liver damage. No other cause known
34P	15	17	Eight young born	Young died first day	Mother died 8 days later

TABLE III. THE EFFECT OF JAUNDICE ON THE REPRODUCTION IN THE ADULT RAT
Group III. Animals Operated on at Various Stages of Pregnancy But Bile Duct
Was Not Ligated or Sectioned

RAT NO.	STAGE OF PREGNANCY AT WHICH OPERATED (DAYS)	OUTCOME	WEIGHT OF YOUNG	REMARKS
74B	4	Normal litter	Normal	Mother cared for young normally
75P	5	Normal litter	Normal	Mother cared for young normally
76W	10	Normal litter	Normal	Mother cared for young normally
77	10	Normal litter	Normal	Mother cared for young normally
78	11	Normal litter	Normal	Mother cared for young normally
79B	14	Normal litter	Normal	Mother cared for young normally
80	15	Normal litter	Normal	Mother cared for young normally
81	15	Normal litter	Normal	Mother cared for young normally
82B	17	Normal litter	Normal	Mother cared for young normally
86W	18	Normal litter	Normal	Mother cared for young normally

The results obtained from the three groups are shown in Tables I to III. Data on only those animals which lived for a sufficient length of time are reported. The members of Group I were placed with males of tested fertility forty-eight hours after the operation. Daily vaginal smear examinations were made during the next thirty days. The vaginal cycle was normal, yet in all cases the animals failed to breed. The females were then separated from the males and vaginal smear examinations were continued. When the smear test showed the animals to be in heat, artificial fertilization was attempted by injecting a portion of a buchanal plug obtained from a normal mating. This succeeded in only one case (Rat 8). She died fifteen days later. Autopsy showed six well-developed embryo. We can conclude that jaundiced rats fail to breed normally and this failure is not due to an upset in the vaginal cycle.

Group II included 20 animals operated on at various stages of pregnancy. The results show (see Table II) that induction of icterus during the first ten days of pregnancy was invariably fatal to the embryos, resorption taking place. Those animals which were operated on between the tenth and fifteenth day of pregnancy (with the exceptions of Rats 12 and 15 where resorption took place) gave birth to young which were, however, from 20 to 30 per cent underweight. The mothers invariably failed to care for the young. Both the mothers and the young died shortly after the end of the period of gestation. In all cases the liver and kidney damage was very marked.² Pregnancy added an additional strain to the badly taxed organs. These factors probably account for the death of the mothers who were invariably very much emaciated at the end of the period of pregnancy.

The question arises: are the young born to jaundiced mothers also jaundiced? This point was tested in the following manner: young rats obtained from normal mothers as well as rats obtained from mothers jaundiced between the eleventh and eighteenth day of pregnancy were tested for total bilirubin content. One animal was used for each determination. The body of the rat was placed in a mortar with 20 c.c. of 95 per cent alcohol and finely ground. The mixture was then filtered, and the bilirubin content was determined with the aid of the van den Bergh reaction.³ A distinct gradient was found, the color being least in the

young obtained from normal mothers and greatest in those young whose mothers were operated on at the earlier stages of pregnancy.

The fact that the young born to icteric mothers were likewise jaundiced probably contributed to their underdeveloped condition and their low body weight. However, the toxic condition of the icteric mother which resulted in damage to the liver and kidneys was undoubtedly a factor of first importance in determining the condition of the young at birth.

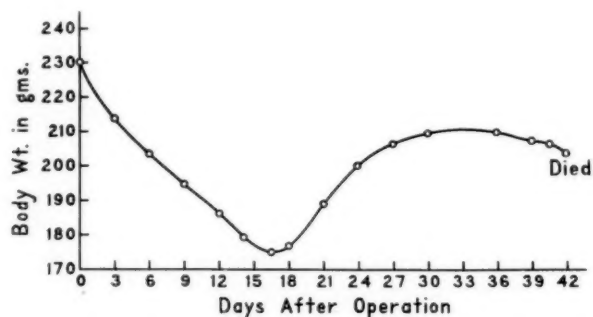


Fig. 1.—Graph showing typical changes in body weight in jaundiced adult nonpregnant rat.

Group III consisted of 10 pregnant animals operated on at various stages of pregnancy as shown in Table III. In this case the operation was performed just as in the other cases with the exception that the bile duct was not sectioned nor ligated. This group of animals served as a control to determine the effect of the operation. The results (see

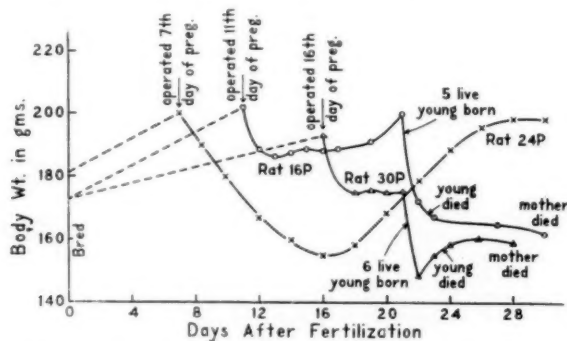


Fig. 2.—Graph showing the body weight curves of rats jaundiced at various stages of pregnancy.

Table III) show that all of the animals completed their periods of gestation normally. We can thus rule out the effects of the operation and attribute the abnormal effects found in Group II to the icterus.

It is to be noted that Rats 1008, 12 B, and 29 (see Table I) recovered from the jaundice at the end of about thirty days, as shown by the disappearance of bile pigments in the urine and a return of the normal pink color to the eyes and ears. These rats were continued on

the experiment. Rat 29 gave birth to a normal litter which at the age of twenty-five days appeared normal. Their body weights were also normal. The other two failed to breed. Autopsy on all three animals failed to show a communication into the duodenum. The bile duct in all cases was swollen. These results can only be explained by assuming that the bile entered the duodenum through one or more tiny fistulous tracts even though it was impossible to demonstrate their presence. Andrews and Dostal⁴ have reported a similar case in a dog.

Typical body weight curves for the members of Groups I and II are shown in Figs. 1 and 2. In Group I after operation there was a marked and continued loss of body weight during the first sixteen to eighteen days. This was then followed by a rise. The curve returned to the initial point or above. Autopsies performed during this stage showed the common bile duct to be swollen to enormous proportions. The bile thus collected accounts for the large gain in body weight. Fig. 2 shows typical body weight curves for the members of Group II.

CONCLUSIONS

1. Jaundiced female rats will not breed. 2. The vaginal smear picture in the icteric rat is normal. 3. In one case of successfully induced artificial fertilization the gestation failed due to overtaxing the mother. In the other 10 cases artificial fertilization failed. 4. Resorption takes place in rats in which icterus is induced during the first ten days of pregnancy. 5. In rats jaundiced later than the tenth day of pregnancy the gestation may succeed, but the mother usually neglects the young and dies shortly after the birth of the litter. 6. Rats born to jaundiced mothers are from 20 to 30 per cent underweight. They are likewise jaundiced. 7. Three instances in which icteric rats apparently recovered from the jaundiced condition are reported.

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DELIBERATE RUPTURE OF THE MEMBRANES EARLY IN LABOR

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SOME interesting observations on the terrors of so-called "dry labor" were made by Schultze¹ in a study of over 600 cases. The incidence was 9.3 per cent of hospital deliveries, and was more frequent in primiparas than in multiparas. Contracted pelvis was not more common than in the control group, but abnormal presentations were $3\frac{1}{2}$ times as frequent. The incidence of interventions was slightly higher, but two-thirds of the women would have needed assistance even if the membranes had been intact. The morbidity was slightly higher, but explainable by the large number of interventions. Fetal mortality was identical. The most striking finding was that the duration of labor was considerably shorter than the average, namely, 12.1 hours in the primipara, and 7.1 hours in the multipara. It would thus appear that the loss of the amniotic fluid is not by itself serious.

The rôle of the bag of waters, following the teachings of Bumm, is usually given as that of a hydrostatic wedge, but so many objections have been raised on the basis of clinical observation, and so deviously have they been explained away, that much of the force of the theory has been lost. A different hypothesis, one which more nearly fits clinical experience, is offered by Kreis² of Strasbourg on the basis of the microscopic study of the cervical tissues. He maintains that the bag of waters, although vital for gestation, is unessential for the progress of labor. Instead of the forewaters (so many times absent) it is the hard head (and less efficiently the softer breech) of the child which offers the resistance against which the uterine contractions may exert their efforts. The tangentially arranged fibers of the cervix, capable of distention and internal rearrangement, are gradually pulled upward into the lower uterine segment producing first obliteration and then dilatation of the cervical canal because of their obliquity to the obstruction ideally offered by the child's head.

To test his theory he instituted the practice of rupturing the membranes of all women in definite labor as soon as they presented themselves at the hospital, regardless of abnormalities. He noted³ a definite increase in the frequency and strength of the contractions, and the progress of labor was hastened. So frequently did floating heads engage after the rupture of the membranes that he was led to suggest that the bag of forewaters might constitute a cause of dystocia. The work was repeated and confirmed by LaHaye.⁴ A study of the protocols of a total of 761 cases with about twice as many controls shows convincingly that the duration of labor was markedly shorter than that found in any hospital practice or textbook description. This is all the more significant when it is realized that rupture was performed with absolutely no discrimination other than that the woman be in labor.

In analyzing both series of cases, LaHaye found that the fetal mortality was identical, the morbidity slightly lower, and the incidence of interventions decidedly lower.

The author was led to this study, which involves 500 cases, by the excellent results obtained by him with the castor oil, quinine, and rupture of the membranes method of inducing labor, together with the satisfaction expressed by many authorities in this country and in Great Britain with simple rupture of membranes. It was decided to limit the experiment to normal uncomplicated labors only, and the internes at Charity Hospital were instructed to perform the procedure on all women on one obstetric service who came into this category. At the same time a smaller series was started among women delivered at home by students under the supervision of members of the staff of the Hutchinson Memorial Clinic. The following types of cases were excluded: premature labor, induced labor, contracted pelvis, toxemia, hemorrhage, abnormal presentation (including breech), dead fetus, hydramnios. Thus only perfectly normal women in definite labor with vertex presentations were considered, and 200 cases of deliberate rupture of the membranes are available. For controls 200 women in the same situation delivered by the same men under the same conditions during the same period of time are presented. Finally 100 similar cases of spontaneous rupture of the membranes within twenty-four hours before the onset of labor are added for comparison.

The duration of labor is calculated from the time the women came under observation, and no case is included where the dilatation was greater than 3 fingers. It was felt that the time of the onset of labor is so indefinite with most women that the total duration is valueless for statistical purposes, but by recording the exact degree of dilatation at the time the women came under scrutiny a more accurate study could be made. Although the figures for the duration of labor, therefore, are not comparable with other clinical reports, the experimental and the control groups may be justifiably contrasted. The standard of morbidity was 100.4° F. temperature for any one day, not including the first after delivery. The distribution of colored and white patients, and the distribution of occipitoposterior positions was almost exactly equal among the two groups.

All cases reported here were taken serially, but in addition to the exclusions mentioned above, 6 women whose labors extended over eighteen hours after observation are not listed on the grounds that some unrecognized pathology was present. Of the 6, one was in the experimental group, one in the classical "dry labor" group, and 4 in the group with intact membranes until complete dilatation.

There were only 3 fetal deaths altogether: one in a woman whose membranes ruptured spontaneously on admission to the hospital and

in whom the umbilical cord prolapsed two hours later, and two in the "intact" group, one a forceps delivery with death on the fourth day, and one an unexplained intrapartal death.

Table I gives the average length of time in hours between the direct observation of the patients and the delivery of the child, the number of cases being in parenthesis. The interventions and the infections are given in Table II.

TABLE I. DURATION IN HOURS FROM OBSERVATION TO DELIVERY

	TWO FINGERS		THREE FINGERS	
	PRIM.	MULT.	PRIM.	MULT.
Intact membranes	(60) 6.5	(76) 5.0	(32) 4.9	(32) 3.6
Premature rupture	(35) 5.1	(37) 3.7	(9) 2.6	(19) 2.1
Experimental	(66) 4.4	(57) 3.2	(28) 3.6	(49) 2.2
Total "dry"	(101) 4.6	(94) 3.4	(37) 3.3	(68) 2.2

TABLE II. INTERVENTIONS AND MORBIDITY

		INTERVENTIONS	INFECTIONS
Intact membranes	(200 cases)	(25) 12.5%	(56) 28%
Premature rupture	(100 cases)	(7) 7.0%	(21) 21%
Experimental	(200 cases)	(19) 9.5%	(32) 16%

Thus it is seen that in a group of women entering a hospital (or visited in the home) with normal uncomplicated, definitely progressing labor, the average time remaining until delivery of the child can be shortened from 6.5 and 5.0 hours to 4.6 and 3.3 hours in the primiparas and multiparas, respectively, at two fingers' dilatation. At three fingers' dilatation the average duration can be cut from 4.9 and 3.6 to 3.3 and 2.2 hours, representing in all groups a saving of about one-third the remaining period of labor. The procedure of rupturing the membranes is not only harmless but salutary, for infection and interference are both reduced by about a third and the fetal mortality is unchanged.

The question is often asked: "Why shorten labor?" The answer, fortified by the results of this study, is briefly: To conserve the woman's strength. She is better able to undergo the second stage, which obviates frequently the use of forceps; less intrauterine invasion means less infection. She is in better condition to resist infection in the absence of manipulation. If the labor is shorter the cervix is wide open for a shorter period of time and there is less opportunity for bacterial invasion, because it is recognized that the percentage of infections rises with the duration of labor.

Two arguments have been adduced against the proposed procedure: one, that the membranes act as a barrier to infection. In the first place, clinical evidence as cited above is to the contrary, and second, the chief statistical support relates to cesarean section deaths. Although such

death rates are higher when the membranes have been ruptured, it is suggested that in most of such cases it is the accompanying long labor with frequent vaginal examinations rather than the absence of the amniotic sac that is responsible. The other objection is the possible damage to the baby's head if unprotected by the amniotic fluid. Again, there is no scientific evidence to support the objections or to show that babies of "dry labors" produce a larger percentage of idiots in later life than their moist-born contemporaries. Surely it is swallowing the camel and straining at the gnat to conceive of a baby's head, crushed by the pelvic bones to the point of molding, suffering from scalp pressure of the cervix. It might be remarked finally that caput succedaneum or asphyxia were not reported with any greater frequency in the experimental group than in the control group.

CONCLUSIONS

1. A study is presented of 500 consecutive uncomplicated labor cases at term, in 100 of which the membranes ruptured at the onset of labor and in 200 of which the membranes were deliberately ruptured at 2 or 3 fingers' dilatation.
2. There was, as a consequence, a shortening of labor by about one-third the remaining time to delivery, resulting in a conservation of the woman's energy.
3. The fetal mortality was unaffected.
4. The percentage of interventions was reduced nearly a third.
5. The morbidity was reduced by more than a third.
6. This simple and innocuous procedure, which spares the woman, reduces the frequency of forceps application, and lowers the rate of infection, is applicable both in hospital practice and in home deliveries.

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SMALLPOX VACCINATION OF THE NEWBORN

REPORT ON 808 ATTEMPTS

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DURING 1931, because of the numerous cases of smallpox reported in Iowa, it was decided to vaccinate all patients admitted to the University Hospital with no evidence of successful inoculation. Sometime later, in an attempt to provide immunity for a still larger part of the population, the vaccination of newborn children was begun and is still in force. This study records results obtained up to May 7, 1933.

Vaccination is recorded as having been done in 808 out of 1,041 babies born between Jan. 1, 1932, and May 7, 1933. Soon after the work was started, it became evident that the reactions obtained in premature infants were unusually severe and thereafter such babies were not inoculated. In certain other instances vaccination was not performed or was unrecorded.

The inoculations were made in the delivery rooms before the babies were removed to the nursery. The skin at the chosen site was cleansed with ether. Multiple acupunctures were made through a drop of vaccine placed on the skin, and, after a moment's wait, the excess vaccine was removed by light pressure with a gauze sponge. Eli Lilly Company's stock preparation "V5 Ampules" was employed. Six boxes (30 tubes) were obtained from the pharmacy at each order and were kept in the delivery room (average temperature 80° F.) until used—ordinarily about two weeks. Throughout the earlier and greater part of the period, males were vaccinated on the arms and females on the thighs. When a preliminary survey of the results indicated that the boy babies (arm inoculations) had a smaller percentage of "takes," it was decided (March 1, 1933) to use the thighs of both sexes in order to determine, if possible, whether the variation was due to a sex difference or to the site employed. The vaccinations were done by some forty individuals.

The children were studied as to the presence or absence of a "take," and to the weight gain during the first eight days of life. Other factors noted include: the incidence of conjunctivitis, impetigo, and thrush, the course of the temperature curve, and the maternal Wassermann reactions. The seventeen-month period was studied as a whole, but it was noted that until July 1, 1932, the records lacked the uniformity which obtained after that date, and a second compilation considered the entire data from that day to May 7, 1933. Since all vaccinations after March 1, 1933, were made on the thigh, the last ten-week interval was surveyed as a unit (Table I).

TABLE I. THE PERCENTAGE OF POSITIVE REACTIONS

	MALES	FEMALES	AVERAGE
Entire period	29.0	35.5	32.2
July 1, 1932, to May 7, 1933	31.8	40.3	36.0
March 1, 1933, to May 7, 1933	40.6	51.2	45.3

There were more males (417) than females (391) in the series, but the percentage of "takes" is consistently higher in the latter. It is also evident from Table I that the percentage of positive reactions increased in the latter part of the period. During the months under consideration there was a gradual increase in the number of deliveries, which tended toward the employment of fresher vaccine. Table II gives the total deliveries by months.

TABLE II. TOTAL DELIVERIES BY MONTHS

January, 1932	51	September, 1932	62
February	62	October	70
March	44	November	60
April	57	December	60
May	51	January, 1933	76
June	64	February	77
July	71	March	104
August	61	April	71

In the period after March 1, 1933, all vaccinations were made on the thighs, but this period also showed the greatest number of deliveries, and it is difficult to state which factor was responsible for the greater percentage of "takes." Since the increase of "takes" in females is as great as that in males, it would seem that the freshness of the vaccine is more important than the site of inoculation. It seems quite definite, however, that girls are generally somewhat more susceptible than boys.

Study of the weight charts gave the data as shown in Table III, indicating that positive reactions have no significant effect upon the weight gain during the first eight days of life.

TABLE III. THE EFFECT OF VACCINATION ON THE WEIGHT EIGHT DAYS AFTER BIRTH

GROUP	ABOVE BIRTH WEIGHT		BELOW BIRTH WEIGHT		AT BIRTH WEIGHT		TOTAL
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	
Female positive	39	28.2	99	71.2	1	0.6	139
Male positive	37	31.4	84	68.6	0	--	121
Female negative	69	27.3	178	70.6	5	1.2	252
Male negative	102	34.5	190	64.3	4	1.4	296
Female total	108	27.6	277	70.8	6	1.5	391
Male total	139	33.3	274	65.7	4	1.0	417

The three most common infections during the first eight days of life are:

1. Acute catarrhal conjunctivitis, unilateral or bilateral, with a sero-purulent discharge, in which mixed organisms, or occasionally pneumococci, are found. It appears usually on the sixth or seventh day after birth.

2. Impetigo, with small superficial blebs frequently appearing first under the arms and then spreading to the abdomen, face, and hands, evidently by contact.

3. Thrush, a fungus infection, contracted at birth from the infected vaginal discharge of the mother, or later from other sources.

TABLE IV. THE EFFECT OF INTERCURRENT INFECTIONS UPON THE WEIGHT GAIN

TYPE OF INFECTION	SEX	VACCINATION RESULT	NUMBER OF CASES	GAINED WEIGHT	LOST WEIGHT	PER CENT GAINED
Nonspecific conjunctivitis	F	Negative	27	5	22	
	M	Negative	24	6	18	
	F	Positive	12	2	10	
	M	Positive	8	6	2	
Total			71	19	52	26.7
Impetigo contagiosum	F	Negative	12	2	10	
	M	Negative	15	4	11	
	F	Positive	5	3	2	
	M	Positive	4	1	3	
Total			36	10	26	27.7
Thrush	F	Negative	10	3	7	
	M	Negative	6	1	5	
	F	Positive	8	1	7	
	M	Positive	1	0	1	
Total			25	5	20	20.0

There was no significant alteration in the weight curves of babies with conjunctivitis or impetigo, but the presence of thrush, as might be expected from the occasional difficulty in nursing, interfered with the regaining of birth weight, irrespective of the result of the vaccination.

TABLE V. TOTAL INCIDENCE OF THE THREE INFECTIONS

CASES	NO.	CONJUNCTIVITIS		IMPETIGO		THRUSH	
		NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
All cases	808	71	8.78	36	4.45	25	3.09
Vaccination pos.	260	20	7.69	9	3.49	9	3.49
Vaccination neg.	548	51	9.3	27	4.92	16	2.91

PERCENTAGE INCIDENCE OF THE THREE INFECTIONS IN RELATION TO THE VACCINATION RESULT

DISEASE COMPLICATION	POSITIVE VACCINATION		NEGATIVE VACCINATION	
	NO.	PER CENT	NO.	PER CENT
Conjunctivitis	20	7.7	51	9.3
Impetigo	9	3.5	27	4.9
Thrush	9	3.5	16	2.9

There is no significant variation in the incidence of these three infections depending upon the result of the vaccination.

In the positive cases, pustules 5 to 12 mm. in diameter usually appeared on the fourth to the seventh day. There was commonly an enlargement of the regional lymph nodes on the side of the vaccination, and frequently those of the opposite side were involved to a lesser degree. Enlargement of the spleen was not noted, although several cases have been reported in the literature, in which splenomegaly occurred at the height of the cutaneous reaction, but subsided rapidly. Eight of the 260 infants with "takes" developed a wide inflammatory reaction in the surrounding tissues, and in one instance there was considerable ulceration at the vaccination site with "transplant" pustules around the anus. One infant, having a positive reaction, developed a parotid abscess, which was incised and drained, and also had thrush, impetigo, and pylorospasm. Since these complications all appeared within the first five days, they can probably be viewed as coincidental.

In the majority of positive cases, the temperature curve was not disturbed, but in a few instances fever up to 102° was present for two or three days in the absence of other demonstrable causes.

It is interesting to note that among 24 infants of syphilitic mothers (positive blood Wassermann reactions) only two had positive reactions.

Camus¹ has noted that the freshness of the vaccine is an extremely important factor, especially in very young infants (ten days to three months of age). His results may be summarized as shown in Table VI.

TABLE VI. POSITIVE REACTIONS (PER CENT)

AGE OF CHILDREN	FRESH ACTIVE VACCINE	OLD VACCINE
Above six months	100.0 per cent	96.5 per cent
Three to six months	92.6 per cent	70.3 per cent
Less than three months	84.4 per cent	24.0 per cent

Schwartz⁶ confirmed the tendency toward a low percentage of positive reactions in smallpox vaccinations and in the Schick and Dick tests among infants and particularly during the first month of life. Upon comparing the observed results with the amount of antibody he could detect in the blood, he concluded that the immunity is not humoral in character but is a property of the skin itself.

SUMMARY

In poorly vaccinated communities, the vaccination of newborn infants offers a method for increasing the number of relative immunes in the population. There is practically no danger associated with the inoculation of mature infants immediately after birth, but reactions

are apt to be more severe in prematures, and it is advisable to postpone vaccination until they are gaining satisfactorily.

The percentage of "takes" depends largely upon the freshness of the vaccine, but girls seem more susceptible than boys, and more positive reactions are obtained on the thighs than on the arms.

Positive reactions do not adversely affect the weight curve, and rarely cause elevations of temperature. Moreover, they are not affected by, nor do they affect, the incidence or course of the common intercurrent infections—conjunctivitis, thrush, and impetigo. Children of mothers with positive blood Wassermann reactions rarely show "takes."

CONCLUSIONS

Attention should be given to the advisability of routine smallpox vaccination of healthy, mature children at birth, especially in areas where the nonimmune proportion of the population is high.

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AN ANATOMIC STUDY OF A MAMMARY GLAND TWENTY-FOUR HOURS POSTPARTUM

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DESCRIPTIONS of anatomic studies of the mammary gland in the literature are few. Ninety years ago Cooper published drawings of dissections made after injecting the mammary ducts at the nipple. These fail to show definitely certain ducts which terminate blindly. Andrews and Kampmeier published a wax reconstruction of a gland in a fifteen-year-old boy which shows only ducts which terminate blindly.

My studies were made of breasts from a primipara aged twenty-seven years, who died twenty-four hours postpartum, in which blind ducts were demonstrable. I was able to demonstrate two types of ducts: one group, beginning at the periphery of the nipple, developed lobules soon after leaving it; the other group went out from the center of the nipple, developed branches by means of finger-like processes of the ducts, to the third and fourth order, without terminating in lobules. These blind ducts, in the cow, have been shown to serve as reservoirs for milk. It is possible that perversion of this function may lead to formation of the cysts we find in human breasts.

I was also able to demonstrate lobules connected to the suspensory ligament by three fibrous tissue bands carrying blood vessels. It is logical to assume that traction on these bands caused by carcinoma of the breast is responsible for dimpling and retraction of the skin in that disease.

GENERAL STRUCTURE OF THE BREAST

The body of the breast studied, presented anteriorly a circular mass of tissue which was almost as thick at the periphery as in the center.

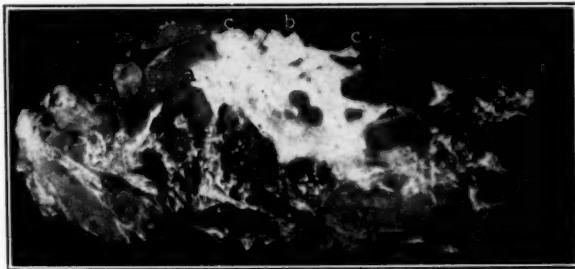


Fig. 1.—Cross-section of mammary gland twenty-four hours postpartum. Fibrous body, *a, a*; site of nipple, *b*; areola, *c, c*.

In front it was covered by a layer of fat, the fat capsule of the breast, which had been continuous with the fat layer covering the body. It was absent at the nipple and behind the areola (Fig. 1). The posterior surface was slightly concave and all irregular areas due to the shape of lobes of glands were filled with fat.

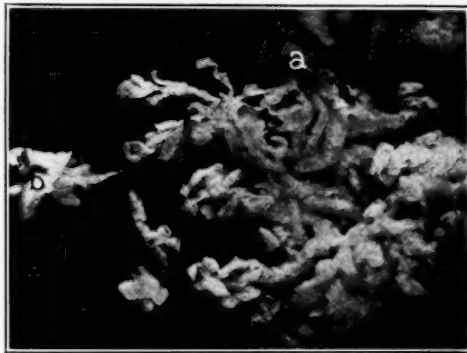


Fig. 2.—Peripheral system of ducts and glands, $\times 2$. Region of nipple site, *a*; ducts and lobules contained in 1 cm. of fibrous body, *b, b*.

Removal of the fat layer, also cross-section of the gland disclosed the fibrous body. This is presented in Fig. 1 in which the central portion appears to be fibrous tissue pierced by the cut sections of ducts. Dissection of this area (Fig. 2) showed that very little of this tissue was fibrous, but was made up of ducts and lobules of acini, so closely packed that one lobule was closely adherent to a lobule of a neighbor-

ing duct or took a longitudinal position next to its own duct. There was no more fibrous tissue, in proportion between these ducts and gland structures than is shown as strands between the fat and acini beneath. The structures illustrated (*b, b*, Fig. 2) were included in not more than 1 c.c. of tissue.

Strands of dense connective tissue were arranged in a radial manner from the nipple to the periphery of the gland and extended from

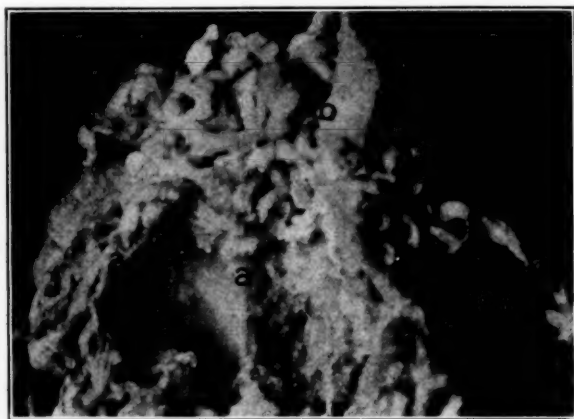


Fig. 3.—Ligaments of Cooper, *a, a*, are shown dissected under the sheath of the nipple, *b*.



Fig. 4.—Longitudinal section of termination of duct located at periphery of nipple.

the skin to the fascia over the pectoralis muscle. These fibrous bands are the ligaments of Cooper. It is in compartments lined by these ligaments (Fig. 3) that a single central duct with its ramifications is housed. Just beneath the nipple, the ducts were separated from each other by a dense cribriform connective tissue. The greater the distance from the nipple, the less dense the fibrous tissue became and more fat was intermingled.

SPECIAL STRUCTURES OF THE BREAST

Ducts and Acini.—A flat, fibromuscular sheath which lay beneath the nipple served as a support for two kinds of ducts which entered the nipple. It served also as their sphincters. The one kind, seven in number, were milky-white, extended from the periphery of the nipple and branched a very short distance from it. Clusters of acini terminated these ducts or extended from their sides (Fig. 2). A longitudinal section of these structures shows their relationship (Fig. 4).

The other kind, also seven in number, pierced the central portion of the fibromuscular sheath and were more transparent in appearance for over half their course (Figs. 5 and 6). These were not more than 1 mm.

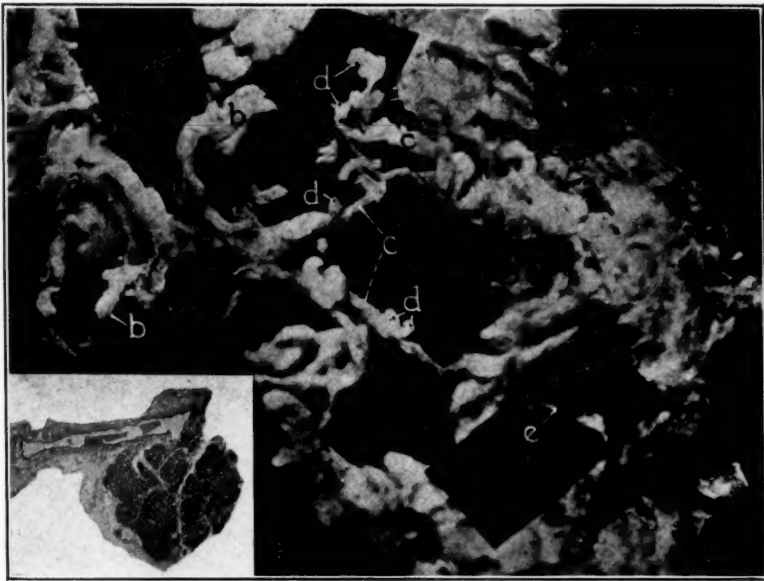


Fig. 5.—Central system of ducts and glands. Fibromuscular sheath of nipple, *a*; ampulla and terminal ducts beneath nipple, *b, b*; ducts from lobes, *c, c*, with lobules, *d, d*, attached to them. Ducts and lobules extending from one lobe to an adjoining one, *e*. Insert, microscopic longitudinal section of *c*, and *d*.

in diameter where they pierced the supporting sheath, gradually widened, in the course of 1 cm., to 2 mm. in diameter and then a slight constriction was found. This dilatation is called the ampulla (*b*, Fig. 6). Another gradual dilatation to 3 mm. occurred in the next centimeter of duct, and it was at this point that four duct structures united with the central duct.

Three of these structures had the gross appearance of sprouts and were composed of numerous ramifications extending to the third and fourth order (*c, c*, Fig. 6). No acini were present as far as gross appearance was concerned, and longitudinal section microscopically confirmed this impression. Repeated sections failed to show acini, but

did show new ramifications formed by finger-like projections (insert Fig. 6). One branch entered directly from a lobe situated toward the center of the base of the gland.

The continuation of the main duct soon received two ramifications of sprouts, and distal to these, 5 ducts entered the main duct at different levels. These ducts came from the lobes of acini at the periphery of the base of the breast (*c, c*, Fig. 5) and had the same whitish appearance as the ducts which entered the nipple at the periphery. Some ducts connected several lobes and then united with a main duct. Single, double, or triple lobules extended from the sides of these ducts at comparatively distant levels (insert Fig. 5). These same individual groups of acini on the same kind of ducts communicated in the periphery of the gland, one lobe with another (*e*, Fig. 5).

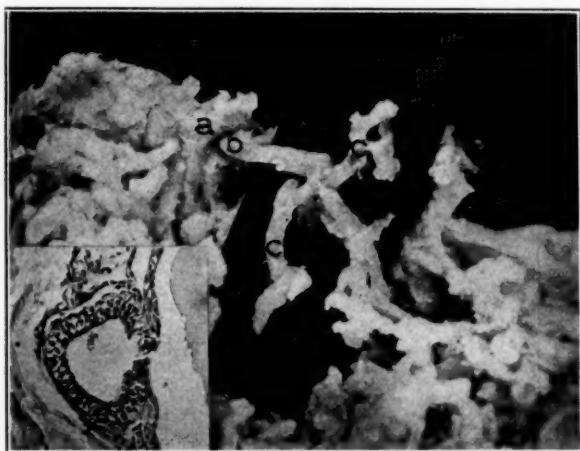


Fig. 6.—Centrally located duct near nipple. Fibromuscular sheath of nipple, *a*; ampulla; *b*; branching of ducts to third and fourth order, *c, c*. Insert, microscopic picture of duct wall shows origin of a new branch.

The entire structure above described was separated from other structures of the same kind by sheaths of the suspensory ligament. One very small duct extended from a lobe on one side of a suspensory ligament to a lobe on the other side.

The lobes of acini at the base were difficult to separate completely. Each had a pyramidal form, and 36 apices were readily counted. Numerous lobules made up a lobe. These lobules were closely united by ducts to the sides of a duct which ramified somewhat tortuously and both structures made up the lobe.

The collecting ducts extended principally from the apex of the lobes; however, the interlobar connection (*e*, Fig. 5) manifested itself toward the central portion of the gland tissue at the base as well as in the periphery.

The method of development of new acini appears to be by finger-like projections which extend from existing acini as shown in Figs. 4 and 8.

Connective Tissue.—Repeatedly, in the dissection, a lobular-shaped structure was observed attached to the suspensory ligament with three fibrous bands (*c* and *d*, Fig. 7). Other connecting bands, which are



Fig. 7.—Cut edges of suspensory ligaments, *a, a*. Under surface of nipple, *b*; lobule, *c*, attached to suspensory ligament by three fibrous bands, *d, d, d*.

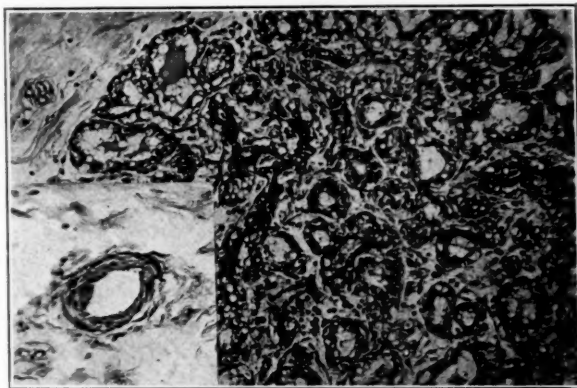


Fig. 8.—Lobule of acini. Section of the structure shown in *c*, Fig. 7. Insert, cross-section of fibrous band in *d*, Fig. 7.

visible in Fig. 7 deeper than the three outstanding ones, could be readily pushed aside by the blunt edge of the scalpel, but the three denser bands had to be cut. Section of this structure (*c*, Fig. 7) showed a lobule of acini (Fig. 8). Sections of the fibrous tissue bands revealed the presence of a blood vessel in each (insert Fig. 8).

COMPARATIVE ANATOMY AND PHYSIOLOGY OF THE BREAST

The presence of duct structures only, and ducts bearing lobules of acini, as well as a combination of these two groups in this breast, ready for lactation, is interesting in the light of the comparative anatomy of the breast. This subject has been ably reviewed and discussed by Turner within the past year.

Among animals, such as the rat and mouse, where the luteal phase of the estrous cycle is either absent or of short duration, proliferation of the mammary gland extends the duct system, with but slight growth of lobules, under the influence of the follicular phase. When functional corpora lutea are present for a considerable period as in the guinea pig, dog, virgin heifers, marsupial dasyurus and the second marsupial or opossum, growth of lobules along the sides of ducts may become quite extensive and approach the development observed during the

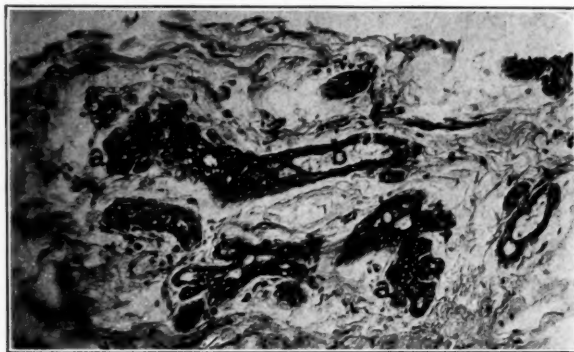


Fig. 9.—Human mammary gland during menstruation shows slight lobule formation, *a, a*, extending from ducts, *b, b*.

first part of pregnancy and in a few animals, the bitch and marsupial dasyurus, during the latter phase of pregnancy.

The initial growth of the mammary gland, including growth of the nipple and duct system, has been shown experimentally to be stimulated by the follicular hormone or hormones formed in the ovary at the approach of and during puberty. Continued stimulation by these hormones causes growth of an extensive duct system with slight lobule formation in some species. The development of the duct system in the human male is explained by the fact that follicular extract is found in the urine of the normal male.

Under the influence of the follicular and luteal extracts, there is further growth of the duct system, and lobule formation and development is stimulated by a succession of estrous cycles, but no evidence of a secretory phase is present. The lobule formation in a human mammary gland removed during menstruation is shown in Fig. 9 and by comparison with Figs. 4 and 5, it is possible to estimate the hyper-

plasia of acini and lobules due to the extended luteal phase of pregnancy. The presence of secretion as shown in these figures is said to be due to hypertrophy of those structures developed during the first half of pregnancy. These secretory changes during the second half of pregnancy in the human female have occurred in the absence of the corpus luteum and are now considered to be under the control of the lactation hormone of the anterior pituitary.

The structure of a duct which pierces the central portion of the fibromuscular sheath of the nipple, composed of ducts and duct ramifications, continuing on to ducts and lobules, and basal lobes, in a breast ready for lactation has not been described to date in the comparative anatomy of the breast.

CLINICAL SIGNIFICANCE

Blue Dome Cysts.—A study of the gross appearance of blue dome cysts has led to the impression that they have their origin in that portion of the central duct system which ends in blind ducts. These cysts are divided into compartments by low ridges or septa of the cyst lining which radiate from a common, rather broad area. One large cyst may be flanked by smaller cysts separated from each other by the same lining septa. One duct and its ramifications as shown in Fig. 6 suggests the origin of one or several adjoining cysts. They are lined by one layer of low cuboidal or flattened epithelium on a basement of flattened spindleform cells which corresponds to the two layers of cells forming the normal duct structure. Gross dissection of the walls of these cysts has shown small lobules of acini with their ducts separated from the cyst wall by fibrous tissue stroma. These lobules are from either the ducts about the periphery of the nipple or from the lobes of gland tissue at the base of the breast.

It is not possible to say from the dissections whether a perversion of function or a mechanical plugging of a duct initiates this process. The lining cells are of those responding to increased pressure rather than to secretory activity. It is interesting to speculate on the possibility of the cysts being initiated by variations in hormonal activity of the ovary and particularly a long follicular phase, since it has been shown that the duct system is extended by follicular extracts. These cysts are most commonly found in patients whose breasts have been sensitive and tender in the premenstrual period for a decade or more.

Retraction of Skin and Nipple in Carcinoma of the Breast.—Adherence of skin to the breast and retraction of the nipple are clinical manifestations of carcinoma of the breast. Increase in the size of acini in functional growth of the breast preparatory to lactation, is concurrent with changes in the fibrous tissue which allow for growth, expansion and mobility of all the breast constituents.

Growth in the acini and ducts due to carcinoma of the breast is also accompanied by changes in the fibrous tissue stroma, but these changes are of a different character than those of functional development as evidenced by the fact that the stroma about many carcinomas is tinctorially that of hyaline degeneration.

Traction on fibrous tissue bands, as those shown in Fig. 7, when of an inelastic character, can readily explain retraction of the skin and also the nipple, for these bands extend to the suspensory ligaments and these will then be retracted secondarily.

SUMMARY

A breast from a primipara of twenty-seven years who died of uremia twenty-four hours postpartum was dissected.

The fibrous body was found to be made up principally of ducts and acini with no greater proportion of fibrous tissue than was found between the lobules, although it was of a denser variety and contained practically no fat.

Three definite fibrous bands connected lobules to the suspensory ligaments, and blood vessels coursed these bands.

Two types of ducts pierced the fibromuscular sheath of the nipple. Those about the periphery soon branched into numerous lobules, and those entering at the central portion were composed of ducts only, with ramifications which appeared as sprouts extending to the third and fourth order.

Development of new ducts and acini is by means of finger-like processes branching from already formed ducts and acini.

The comparative anatomy and physiology of the breast was briefly outlined.

The origin of blue dome cysts is suggested as originating in the central duct system.

Fibrous tissue bands are responsible primarily for retraction of the skin and nipple in carcinoma of the breast.

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CYSTIC SCHWANNOMA OF THE SACRAL PLEXUS

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THE subperitoneal tissues of the pelvis posterior to the broad ligaments, contain a number of important structures. In this cellular area are found the internal iliac arteries, huge plexuses of deep pelvic veins, the ureters, the lumbosacral nerves, the rectosigmoid junction, lymphatics and lymph glands. The approach to this region is difficult. It is a surgical no man's land occasionally invaded by the gynecologist and general surgeon, more rarely approached by the neurosurgeon and orthopedist.

The following case is presented because of its rarity and because of the diagnostic problems involved.

H. N. was admitted to my service at the Mount Sinai Hospital, Dec. 21, 1932, as a case of ectopic gestation. She was thirty years of age, had been married six months; never pregnant. Menstruation which was regular, normal, every twenty-six to twenty-eight days for six days, had begun at the age of twelve years. The last menstrual period had occurred on November 30 to December 5 and ended sixteen days before admission.

The patient had suffered from mild right lower quadrant pain for seven years. Two years ago a small, benign breast tumor (fibroma) was removed at another hospital. One year ago, after an attack of grippe, a numb feeling developed in both legs with "sticking" sensation around the outer side of both calves. In the last three weeks there was increased pain in the right iliac fossa and in the lower lumbosacral region of this side. The diagnosis of ectopic gestation had been based upon dizziness, faintness and fainting spells complained of recently, accompanying the presence of a cystic resistance in the right pelvic region. There were numerous areas of deep pigmentation over the trunk. Hyperactive reflexes were noted, especially exaggerated spasmodic patellar reflexes, amounting almost to clonus. The right thigh and calf were 1 cm. larger in circumference than the left; blood pressure 118/78; hemoglobin 75 per cent; sedimentation time two hours. The urine was negative and contained no Bence-Jones albumin. Blood Wassermann reaction was negative. Spinal fluid Wassermann reaction negative; colloidal gold negative; globulin negative; cell count negative; total protein 34 mg. An x-ray of the pelvis proved negative. The abdomen was moderate in size, without marked spasm or tenderness.

The introitus was normal, nulliparous; the cervix far back, long and conical in shape. A small, anteflexed uterus could be felt in the hollow of the sacrum. The adnexa were normal and readily palpated. Over the right sacroiliac synchondrosis a flattened, resilient protrusion was felt, the portion accessible to the finger being the size of a large plum. Rectal examination showed the mass to be larger, closely attached to the bony structures and radiating upward from the base of the coccyx. Pressure on the mass caused pain to the outer side of the thigh and ankle.

The tumor was recognized as being something of unusual nature due to the fact that the adnexa could be differentiated plainly from the mass.

Neurologic consultation determined that the patient could not stand with her feet close together, that she had a tendency to fall to the right and backward.

On walking she looked downward, took short steps and inclined toward the right and backward. There was a transitory nystagmus on gazing to the right or left. The pupils were slightly irregular, contraction to light was poor but to accommodation was good. There was slight right facial asymmetry. The right knee jerks were greater than the left. The right ankle jerk was normal but the left approached a clonus. There were no definite sensory changes, no motor weakness or fibrillation. Queckenstedt was normal, 80 mm. Hoffmann's sign could be elicited on both sides. Dr. Israel Strauss, Neurologist to Mount Sinai Hospital, concluded that there must be some definite cord involvement, a chronic lesion as yet unlocalized, but in the lumbar region. The ophthalmologist found persistence of the left hyaloid canal. The patient was observed on my service for ten days. A pelvic kidney had been

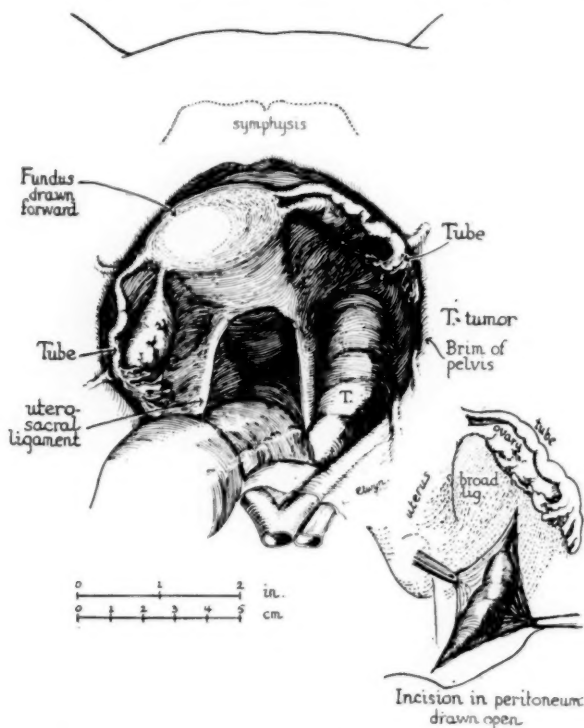


Fig. 1.—Abdomen opened; uterus pulled forward and to left. Insert shows cystic tumor exposed after incision of posterior peritoneum and pelvic fascia.

excluded by intravenous pyelography by means of which Dr. Swick determined that both kidneys were in their normal position.

On December 31, through a right rectus incision the abdomen was opened. A normal uterus and adnexa were found. From the right sacroiliac region and extending along the right pelvic wall, a thin-walled, cystic retroperitoneal mass filled the right side of the pelvic cavity almost to the brim of the true pelvis (Fig. 1). It passed underneath the right broad ligament, raising the normal ovary and tube upward, but had no connection with the uterus or the adnexa.

A longitudinal incision was made through peritoneum and pelvic fascia along the most prominent portion of the mass. Careful dissection, keeping close to the thin-walled cyst, gradually freed it on both sides and anteriorly, exposing the deepest portions of the pelvis. The right broad ligament was pulled forward and upward by means of a retractor. The external iliac artery and vein were in full view

laterally. In intimate contact with the cyst were fibrous bands traversing its surface and imparting to it a pseudo-loculated contour (Fig. 1 insert). The posterior surface of the cyst was found in such intimate contact with the cords of the sacral plexus that the attempt to remove the cyst intact was abandoned. Instead the cyst was opened. Some 5 to 6 ounces of clear amber fluid were evacuated. After collapse of the cyst, its posterior wall was dissected away from the nerve trunks by sharp and blunt dissection. One communicating branch between the fifth lumbar and first sacral had to be sacrificed. During the dissection it was noted that the anterior blunt end of the cyst was cleft, the superficial locule being on the abdominal surface of the obturator internus, the inferior locule entering the sacrosciatic notch below the obturator foramen, accompanying the sciatic nerve for 2 cm. (Fig. 2,

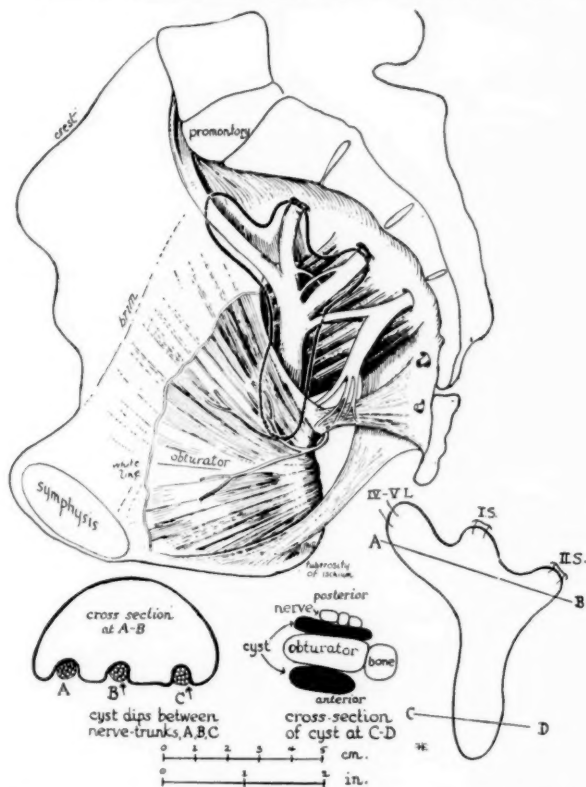


Fig. 2.—Dissection of right pelvic wall showing relation of cystic schwannoma to lumbosacral nerve plexus. Inserts: imaginary cross-sections of cyst at different levels in relation to adjacent structures.

cross-section of cyst at C-D). Although the operation required most careful dissection to prevent injury to the neural structures, there was a remarkable freedom from hemorrhage, considering the numerous arteries and veins situated in this region. Only one large branch going to the external iliac vein and lateral to the cyst required ligation. A clean wound bed remained, in which the sacral plexus, clearly defined, was visible. The pelvic fascia and the posterior peritoneum were then completely closed, and the anterior abdominal wall sutured in layers. The postoperative course was unusually smooth.

The patient, after she left her bed, was transferred to Dr. Strauss's service where careful observation offered no additional data. Neither her general nor local symptoms were modified by the operation.

TABLE I. REPORTED CASES OF PELVIC NEUROMAS (NEUROFIBROMAS)

	AUTHOR	YEAR	SEX	AGE	SITE	CON- SISTENCE	SYMPTOMS	OPERATION	AU- TOPSY	HISTOLOGY	REMARKS
1	Smith, R. W.	1849	M	35	Pelvis, two ant. br. sac.	Solid	Chronic illness	-	Yes	Neuroma	v. Recklinghausen 800 tumors
2	Smith, R. W.	1849	M	32	Pelvis sacral plexus	Solid and cavities 6 x 5 in.	"Gastroenter- itis," pres- sure rectum and bladder	-	Yes	Neuroma	v. Recklinghausen 2,000 tumors
3	Generisch	1870	M	22	P., size child's head	Solid	--	-	Yes	Neuroma	v. Recklinghausen en- tering the sacrosci- atic foramina
4	Williamson and Cripps	1899	F	21	P. fist size	Solid	Pain down the leg	Laparotomy, re- covery	No	Neuroma	
5	Bencke	1901	F	28	P. child's head	Solid	Dystocia, for- ceps	Cesarean section	Yes	Neuroma	Retrorectal
6	Chiari	1901	F	22	P. 2 fist size	Solid	--	Laparotomy, re- covery	No	Neuroma	
7	Verocay	1910	M	31	5th lumbar I & II sac.	Solid	Brain and aud- itory symp- toms	Craniotomy No abdominal op- eration	Yes	Neuroma	v. Recklinghausen tu- mors over sacrum growing into dural sac
8	Breitung	1914	F	29	P. 2 tumors	Solid	Dystocia	Cesarean section	Yes	Neuroma	Invaded both sacroil- iac foramina
9	Versé	1915	F	35	Diffuse pelvic strands	Cordlike solid	Dystocia neg- lected	Cesarean section	Yes	Neuroma	v. Recklinghausen
10	Pok, J.	1916	F	?	Over promon- tory, hen's egg	Solid	Dystocia	Cesarean section Died	Yes		Bilateral over sacro- iliac synchondrosis v. Recklinghausen

TABLE I—CONT'D

	AUTHOR	YEAR	SEX	AGE	SITE	CON- SISTENCE	SYMPTOMS	OPERATION	AU- TOPSY	HISTOLOGY	REMARKS
11	Stoeckel, W.	1923	F	19	Left sacroiliac, size of fist	Solid		Morcelled, recovery (incomplete removal, drainage)			
12	Sippel, P.	1923	F	23	Fist size below promontory	Solid	Dystocia	Cesarean section, tumor by morcellement. Recovery		Neurofibroma partim gangliocellure	
13	Krumbein	1925	M	49	Pelvis	Solid with central hollow	Pressure on rectum	Laparotomy	Yes	Neuroma	Rectum torn causing peritonitis
14	Neumann, H. O.	1927	F	14	P. large	Solid	?	Laparotomy, partial removal	?	Ganglioneuroma	Solid, lifting int. pelvic organs upward
15	Pana	1931	M	52	P. large	Pseudocystic	Old tuberculousis		Yes	Neuroma	50 c.c. thick and necrotic material in central cavity
16	Fels	1933	F	32	Pelvis	Solid	Left sciatic pain	Laparotomy, recovery	No	Unripe ganglioneuroma sympathoblastoma	Ureter had to be mobilized
17	Frank	1933	F	30	Pelvis 5 L. I and II sac.	Cystic thin walled	Numbness and pain in leg	Laparotomy, recovery	No	Schwannoma	Thin walled cyst with clear fluid. v. Recklinghausen

From the location of the growth, particularly its intimate relation to the sacral plexus, the cyst wall, partially enwrapping the fifth lumbar, first sacral, and second sacral nerves in fingerlike projections (Fig. 2, cross-section at *A-B*) and accompanying the beginning of the sciatic nerve, a neural origin was evident. The pathologic report made by Dr. Joseph Globus, neuropathologist to Mount Sinai Hospital, confirmed this.

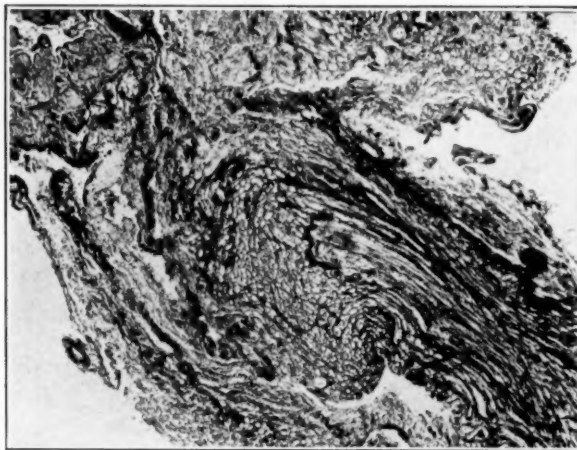


Fig. 3.—Photomicrograph of cyst wall with nerve fibers in the wall. In the center is neoplastic tissue.

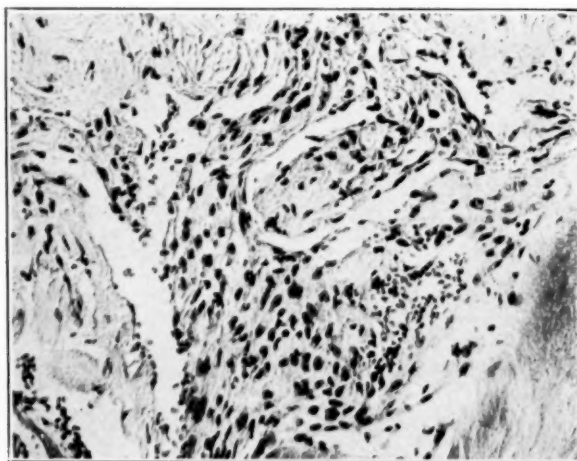


Fig. 4.—Photomicrograph of another area of cyst wall. Island with "palisaded" nuclei of glial origin schwannoma cells).

The thin cyst wall was composed of a connective tissue stroma in which were found medullated and nonmedullated nerve fibers (Fig. 3).

In thicker portions of the wall neoplastic tissue, in direct connection with nerve trunks, showed islands with palisaded nuclei of glial origin (Schwann cells) (Fig. 4).

The cyst, therefore, may be classified as a cystic schwannoma such as occurs with more frequency at the origin of the spinal nerves close to or within the vertebral foramina.

The preoperative diagnosis was aided by the presence of numerous nerve symptoms and the evidence of the v. Recklinghausen's disease. Moreover, both adnexa were readily separable from the mass. Other conditions to be considered were parovarian cyst with unusual location, a cystic subperitoneal fibroid, enlarged pelvic glands, psoas abscess, and finally the unique case of anterior sacral meningocele which was operated upon, drained and followed by fatal meningitis.

Cystic schwannoma, located especially in the intervertebral foramina and within the vertebral canal, are not exceptionally uncommon. They are usually of small size and thick walled.

Careful study of the literature has enabled me to find only 17 cases of pelvic tumors described as neurofibromas, neuromas, or neurinomas with or without accompanying v. Recklinghausen's disease. The majority of these tumors were solid; a few showed larger or smaller cavities resulting from the breaking down of tumor tissue. In only one instance was the cystic cavity lined by a smooth glistening, shining membrane.

Thanks are due to Dr. Robert L. Dickinson for the accurate and expressive Figs. 1 and 2 which were executed under his direction, based on the crude sketches made at operation; also to Dr. J. Globus, neuropathologist of Mt. Sinai Hospital, for the photomicrographs (Figs. 3 and 4).

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10 EAST EIGHTY-FIFTH STREET

BRENNER TUMOR OF THE OVARY

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IN 1907 Brenner described as oophoroma an ovarian tumor which contained two neoplastic elements: (1) ovarian fibrous stroma and (2) columns of branching epithelium histologically somewhat resembling epidermoid lining cells. The origin of the epithelium was erroneously ascribed to the lining cells of the graffian follicle. Under a wide variety of confusing names many writers have reported similar tumors. Frequently too they were erroneously interpreted as true granulosa cell tumors. In 1932, Meyer collected, classified, and clarified 22 cases of Brenner tumor culled from the German literature up to that date. Thanks to this work our knowledge of the Brenner tumor of the ovary now rests upon a secure morphologic and clinical foundation, although the histogenesis still remains somewhat obscured.

The case of Mrs. L. R. (23745), abstracted below, emphasizes the clinical history, gross and microscopic characters of a solid form of Brenner tumor of the ovary. The patient, aged forty-one, was admitted to the Long Island College Hospital, Oct. 26, 1932, complaining of pain in the left lower quadrant and irregular vaginal bleeding. The family and past personal history were irrelevant. Menstruation began at twelve years of age and recurred regularly every thirty days, lasting from three to four days. The last period began Oct. 19, 1932, and persisted until admission to the hospital, seven days later. The patient had been married for twenty-one years and had had one pregnancy twenty years previously. This terminated in a spontaneous and uneventful delivery.

The present illness began in March, 1932, when the patient noted marked vaginal discharge prior to the onset of the menses. The April period was omitted. In May there was profuse menstruation for seven days. The June period was missed but bleeding recurred profusely in the month of July. The menstrual periods in August and September were essentially normal. In August, however, the patient noticed severe pain in left lower quadrant about ten days prior to the onset of menstruation. This became markedly aggravated with the onset of the flow. Since the onset of left-sided pain, there has been associated frequency of urination. The discharge which started in March, 1932, has persisted. Upon admission to the hospital, the temperature, pulse, and respiration were normal. General physical examination was essentially negative. Vaginal examination revealed a lacerated pelvic floor and a slight cystocele. The cervix was lacerated and eroded and from it there came a profuse mucopurulent discharge. The uterus was anteflexed and slightly enlarged. The left adnexa were enlarged to the size of an orange, cystic and only slightly sensitive. There was moderate tenderness in the right fornix, but the adnexa were not palpable.

The laboratory data showed blood pressure to be 100/72, urine normal. Blood count showed red blood cells 4,450,000, hemoglobin 78 per cent, white blood cells 8,500, neutrophils 72 per cent, lymphocytes 28 per cent. Sedimentation time was thirty-seven minutes.

On Nov. 1, 1932, supracervical hysterectomy and bilateral salpingo-oophorectomy were performed. Right and left adnexa were enlarged, subacutely inflamed and

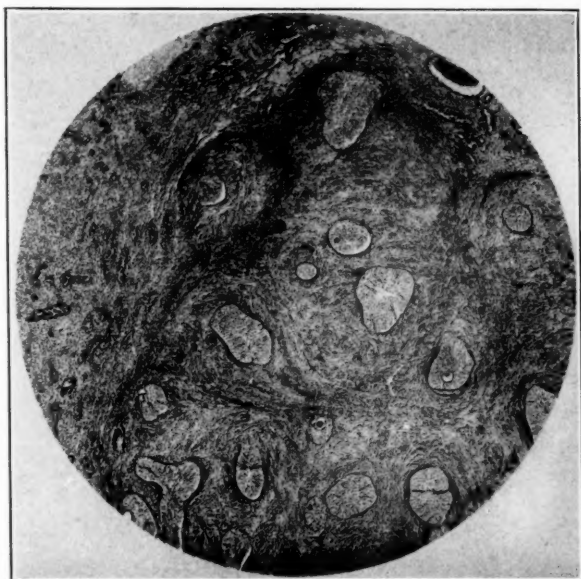


Fig. 1.—Junction of the Brenner tumor with the medullary segment of the ovary. Note the sharp encapsulation at the periphery. The densely hyalinized stroma supports irregular alveoli of epithelium. $\times 80$.

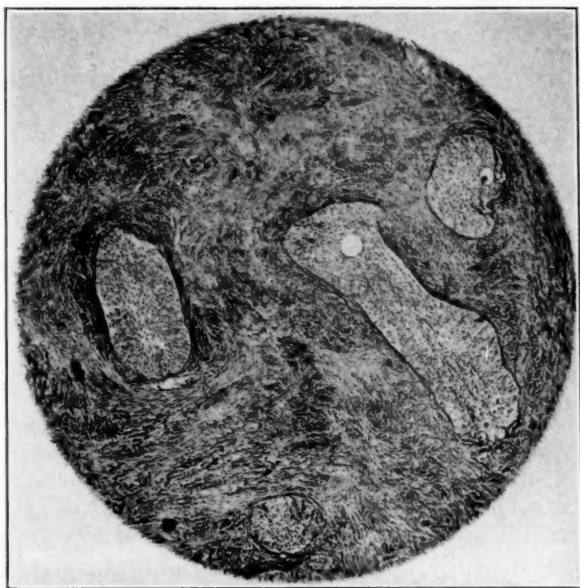


Fig. 2.—The densely hyalinized stroma is characteristic. The epithelial alveoli have been cut transversely and longitudinally. The constituent cell is spindle or fusiform or oval in shape. Centrally the cells lie parallel to the long axis of the epithelial column, at the periphery they course at right angles. Cystic cavities have appeared within the epithelial column. $\times 100$.

adherent to the uterus and broad ligaments. The sigmoid was adherent to the left adnexa. The left ovary, which was enlarged to the size of an orange, ruptured during operative removal. The postoperative course was uneventful and the patient was discharged on the nineteenth day postoperative.

Pathologic examination of the uterus showed a subacute inflammatory endometritis and metritis with chronic perimetritis. There was mild adenomyosis interna. Both tubes were converted into moderate-sized pyosalpinges with thickened walls and dense adhesions. The microscopic examination confirmed the gross diagnosis. The right ovary was normal in size, intimately fused with the tube and broad ligament. Moderate numbers of follicular cysts filled the cortex. Microscopic examination showed chronic interstitial and perioophoritis.

The left ovary was traumatized during surgical removal. As reconstructed it measured 5 cm. in diameter, enlargement being caused by a cyst which presented at

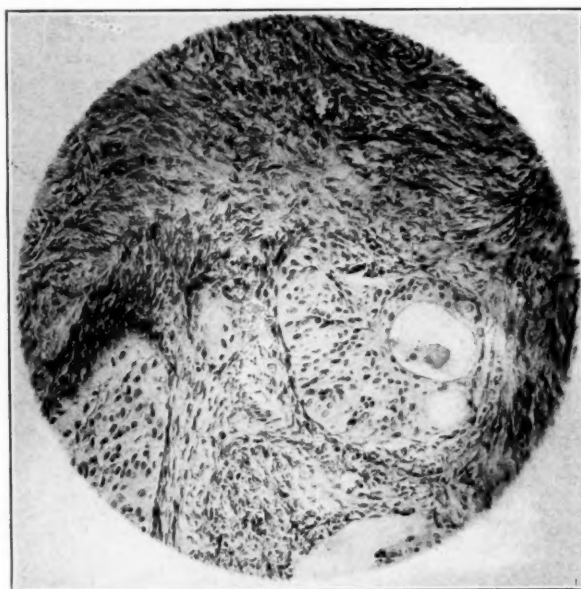


Fig. 3.—The epithelial cells are oval, round or fusiform in shape. The cell membranes are sharply defined. Nuclei are oval and vesicular. Note the cystic areas containing secretion. The tumor cells have been flattened and concentrically arranged about the cavity. The density of the supporting stroma is prominent. $\times 240$.

its inferior pole. This cyst measured 4 cm. in diameter. Smaller follicular cysts persisted in the residual stroma. In the hilum of the organ at the site of the mesoovarium a small oval body was noted measuring 8 mm. in diameter. This was sharply defined, grey-white in color, firm in consistency, and grossly suggestive of fibroma. Microscopic examination of the organ revealed interstitial and perioophoritis with numerous follicular cysts. The large cyst surgically evacuated histologically belonged to the same group. Section through the mesoovarium including the nodule showed changes as follows: The matrix was comprised of densely hyalinized connective tissue arranged in concentric whorls and formed a definite capsule (Fig. 1). The connective tissue stroma supported irregular epithelial cell columns, cut transversely and in their long axis. Transverse sections were round or irregularly oval; the longitudinal sections irregularly cylindrical. Each cell nest was surrounded by a thin but narrow zone of connective tissue concentrically arranged (Fig. 2). The constituent cells were similar in the transverse and longitudinal cell columns, al-

though in the transverse section the radial arrangement of the cells was more striking. In the longitudinal columns the peripheral layers were typically radial in arrangement, the central cells almost parallel to the long axis of the alveolus. The peripheral cells were generally spindle or fusiform in shape and of moderate dimension. The cell membrane was fairly well defined, the cytoplasm of finely granular texture, staining moderately well with eosin. The nuclei were round or irregularly oval in shape, vesicular in character with a fine chromatin network. As the center of the column was approached the cells enlarged, assuming an oval or rounded appearance. The cell membranes became more pronounced; the cytoplasm clear probably due to mucoid or lipoid deposits. At irregular points in the alveoli, vacuolated areas made their appearance. About one-half of the alveoli were so involved. Multiple spaces were not uncommon in the same alveolus, occupying an eccentric or central position. The vacuolated spaces were small, round, or oval. Many were free but as a rule they contained a homogeneous colloid-like substance occasionally intermingled with the nuclei of the degenerating cells (Fig. 3). The spaces were sharply defined by concentrically arranged flattened cells reminiscent of endothelium. Very occasionally a well-defined low columnar epithelial layer was recognizable. The constituent cells were radially arranged, their cytoplasm was occasionally recognizable. In all alveoli mitotic figures are lacking. There is no evidence of malignancy. Nutrition is afforded by scant arterioles.

SUMMARY

A small solid type of Brenner tumor was accidentally discovered in the left ovary removed for a chronic inflammation. The clinical benignity is indicated. The gross appearance similar to fibroma is emphasized. The constituents of the tumor are (1) proliferating stroma (2) columns of branching epithelium containing clear cells with well-defined borders. True and pseudogland spaces in the solid columns are frequent.

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1530 PRESIDENT STREET.

205 HICKS STREET.

ACUTE RENAL FAILURE COMPLICATING PREGNANCY (SYMMETRICAL NECROSIS OF THE RENAL CORTEX)*

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(From the Margaret Hague Maternity Hospital)

ISOLATED case reports have been published in recent years concerning a comparatively rare complication of pregnancy, variously known as symmetrical cortical necrosis of the kidneys, bilateral sequestration of the kidneys, acute renal suppression associated with kidney necrosis, etc. Since Bradford and Laurence first called attention to this entity in 1898 some 41 cases have been reported in the literature, 36 or 86 per cent of these cases coming to autopsy.

*Read at a meeting of the Section of Obstetrics and Gynecology, New York Academy of Medicine, May 23, 1933.

From the excellent pathologic descriptions of observers, such as Jardine and Teacher, Shriver, Oertel, Rolleston, Glynn, Briggs, Kellogg, Klotz and others, the essential lesion consists of a thrombosis of the intralobular arteries with consequent diffuse coagulation necrosis of the cortical tissue supplied.

CLINICAL FINDINGS

Several factors in the clinical histories of these autopsied cases are so characteristic that it is possible to make a diagnosis on the basis of clinical history alone. Although a few isolated cases have been reported as having occurred during the course of certain infectious diseases, these cases of cortical necrosis of the kidneys are almost invariably associated with pregnancy, usually in the middle or third trimester. Until the onset of the characteristic symptom complex the pregnancy appears to be a normal one. There is usually no antecedent history of kidney disease, the patient exhibits no unusual urinary findings, and the blood pressure is not characteristic. The disease is ushered in with evidence of some toxemia of pregnancy. This most commonly takes the form of an abruption of the placenta with retroplacental hemorrhage and almost invariable death of the fetus. Convulsions may or may not be associated with this syndrome and if present are not characteristic. Subsequent to delivery there supervenes evidence of acute renal failure with either partial or complete suppression of urine, and a marked and rapid rise in the values of the metabolites of the blood, i.e., N.P.N., uric acid, and creatinine. The patients appear drowsy, but are easily aroused, except just before death; respirations are slow and not of the Kussmaul type; edema or hypertension may be present but these are neither marked nor constant findings. Death occurs in a very high percentage of cases (86 per cent), and the prognosis depends in great measure upon the completeness of the kidney shut-down. Those patients in whom complete urinary suppression has occurred almost invariably die, the prognosis being more hopeful, however, in those in whom only partial suppression of urine occurs.

In brief, with the pathologic findings of thrombosis of the finer arteries and arterioles of the kidney and necrosis of the cortical parenchyma, there is associated the fairly characteristic clinical picture of a pregnancy suddenly terminated by some placental accident and followed by acute renal failure and azotemia.

CASE REPORT

Mrs. M. C., No. 10882, aged thirty-two years, gravida vi, para ii, was admitted to the Prenatal Clinic 12/17/32. There was no history of previous kidney disease. She had had two spontaneous deliveries and three induced abortions, and now was in the eighth month of a normal pregnancy. On several occasions blood pressure averaged about 122/70; urinalyses were repeatedly negative. She was admitted in labor in the ninth month of her pregnancy (1/27/33), having ruptured the membranes three days prior to admission.

After three hours of rather severe labor, the patient spontaneously delivered a stillborn child. The placenta followed almost immediately, being accompanied by a considerable amount of brown malodorous fluid. On the second day after delivery, the patient developed tenderness in the lower quadrants, became somewhat distended, and was sent to the Septic Ward with a temperature of 104°, with a diagnosis of sapremia and parametritis. She was drowsy, but easily aroused, and manifested a profuse diaphoresis.

On the third day her temperature was normal, diaphoresis was more marked, and the urinary output dropped to 210 c.c.; she was still drowsy but easily aroused, and when aroused was perfectly rational. Urinalysis showed red and white blood cells. On the fourth day, her temperature was 102°; drowsiness persisted; the

blood chemistry showed an elevation of the N.P.N. of the blood to 75, uric acid 6.2, creatinine 1.5; output 1100 c.c. On the fifth day P.S.P. showed 20 per cent total output of dye; diaphoresis was still marked. N.P.N. 75, uric acid 7.5, creatinine 1.7. On the sixth day output dropped to 570 c.c. N.P.N. rose to 107.1, uric acid 6.2, creatinine 2.8. Eyeground examination was negative.

By the tenth day the urinary output had increased to 1260 c.c., the N.P.N. had dropped to 51.3, uric acid 5.3, creatinine 1.6; diaphoresis had ceased. By the twelfth day there was free urinary output, and the patient had decidedly improved, and on the twentieth day N.P.N. was 24.7, uric acid 2.7, creatinine 1.2. The patient was discharged on the twenty-ninth day, the blood chemistry findings being within normal limits. Vaginal examination was entirely negative. Intravenous pyelograms were negative. Throughout her whole illness blood pressures taken almost daily had never risen above 130/70. Last examination on 4/25/33 showed blood pressure 120/70 and a careful examination of the urine showed only an occasional white blood cell and no protein. Vaginal examination was negative and the patient had no complaints.

The treatment included repeated high colonic irrigations, sedatives, and forcing of fluids orally and intravenously.

LABORATORY RECORD

P. P. DAY	OUTPUT	B. P.	BLOOD N.P.N.	URIC ACID	CREATININE	SUGAR	CO ₂	CLINICAL PICTURE
Delivered		120/70	-	-	-	-	-	Temp. norm. No symp.
1st day	-	-	-	-	-	-	-	Same.
2nd day	710	-	-	-	-	-	-	T. 104.6° F. Profuse diaphoresis.
3rd day	210	90/70	-	-	-	-	-	Drowsy but easily aroused. Profuse diaphoresis.
4th day	1100	92/70	75.0	6.2	1.5	75	54	Fluids forced. Glucose intravenously. Hot colonics. P.S.P. 20 per cent.
5th day	1050	120/88	70.5	7.5	1.7	100	60	Eyegrounds negative. Diaphoresis. Drowsy.
6th day	570	120/80	107.1	6.2	2.8	-	-	Same.
7th day	1050	124/64	-	-	-	-	-	Patient brighter.
10th day	1260	128/70	51.3	5.3	1.6	89	44	Sed. time 20 min. Mentally clear.
20th day	Voiding freely	126/78	24.7	2.7	1.2	75	72	Patient bright.
29th day	Voiding freely	120/70	39.0	2.7	1.0	97	48	Discharged home. No complaints. No abnormal findings.
12 weeks 4/25/33	Voiding	120/70	-	-	-	-	-	Intravenous pyelogram negative.

SUMMARY

The case is here reported of a thirty-two-year-old multigravida without history of previous kidney disease, running a normal antepartum course with normal blood pressure and normal urinary findings, who delivered spontaneously after a short, severe three-hour labor, a stillborn fetus and an abnormal placenta in the ninth month of her pregnancy. On the third day following delivery she developed signs of acute kidney failure with partial suppression of urine, a marked, probably compensatory, diaphoresis, a sudden rapid rise in the value of the blood metabolites, all without evidence of mechanical obstruction of the urinary tract, hypertension, edema, convulsions, or vomiting. Except for the fact that the suppression of urine was only partial and of short duration, this clinical picture parallels so closely that described in previously published case reports that a diagnosis of thrombosis of the intralobular arteries of the kidney with symmetrical necrosis of the kidney cortex followed by recovery may justifiably be made.

The results of treatment have been uniformly discouraging. Early decapsulation has yielded as many deaths (3) as recoveries (3), but it is the only active therapeutic procedure available if colonic purgation, intravenous medication, rectal instillations, and sedation fail.

For the use of this material from the Margaret Hague Maternity Hospital we wish to thank Dr. Samuel A. Cosgrove, director, and Dr. Joseph Binder, from whose service this case was discharged.

114 EAST FIFTY-FOURTH STREET

THREE CASES OF PRIMARY CARCINOMA OF THE FEMALE URETHRA TREATED WITH RADIUM

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IN 1922 Milward and I reported one case of primary carcinoma of the female urethra treated with radium, and in 1924 another case similarly treated. I now wish to report three additional cases, and the fact that the patient treated in 1923 is alive with no signs of recurrence at the present time, over nine years later.

CASE 1.—C. G., aged forty-five. The patient was first examined on Aug. 28, 1928, at which time she complained of painful urination and vaginal bleeding. Menstruation had been irregular for one year, the intervals varying from three to five weeks, and the duration of the flow from two days to two weeks. For the same length of time there had been some pain on urination and for the last two weeks urination had occurred about every hour. There was some leucorrhea. She had borne three children but there was no history of lacerations or postpartum infection. There had been a loss of weight of six pounds in the last year.

Examination under the anesthetic showed a slightly relaxed vaginal outlet. On separating the labia a friable, irregularly rounded mass was visible at the site

of the urethra. The urethral orifice could not be seen, but by inserting a glass catheter it was found slightly anterior to the middle of the projecting mass. This globular mass was about 3.5 cm. in diameter and appeared to surround completely

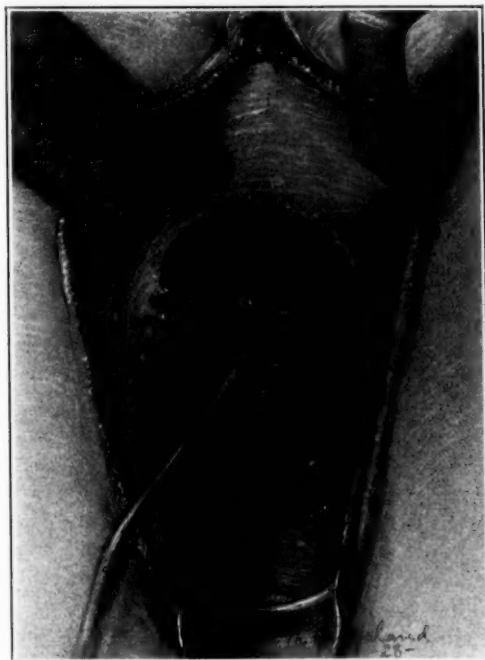


Fig. 1.—Case 1. Carcinoma urethra.

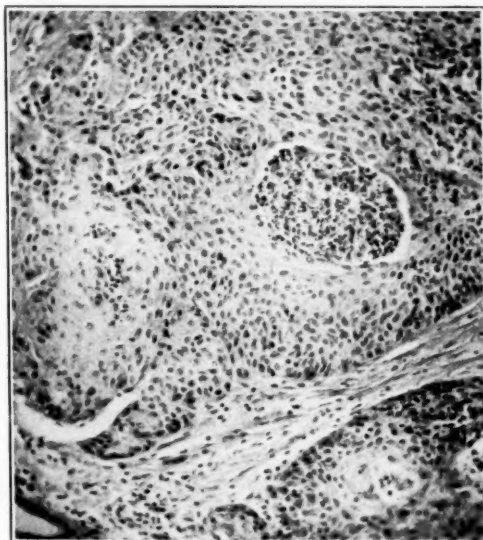


Fig. 2.—Case 1. Squamous cell carcinoma urethra.

the urethral opening. On the right side of the vulva, where this mass pressed upon the wall, there was an ulcerated area about 2 cm. in diameter with slightly raised edges. The cervix was slightly enlarged, the anterior lip being larger than

the posterior. The surface was everywhere smooth. Uterine curettings and a portion of the urethral growth were obtained for microscopic diagnosis. The curettings showed only chronic endometritis but the urethral growth was found to be a squamous cell carcinoma.

On September 1 the greater part of the presenting growth was excised with the cautery, the urethra passing through the remaining portion of the growth very near to the uninvolved anterior vaginal wall. Ten gold implants, each containing 1.07 mc. radon, were inserted in the base left by the removal of the tumor and into the extension on the right side of the vulva. In addition, one 25 mg. tube of radium element, screened with 0.5 mm. silver, 1 mm. brass, and 1.5 mm. rubber, was sutured to the center of the surface of this vulval extension, and one 50 mg. tube, screened with 0.5 mm. silver, 1 mm. brass, and 1.5 mm. rubber, was applied in the anterior urethra. These tubes were left in position eight hours, the total radium dosage being 2,012.4 mg. and mc. hr. or 15.24 mc. destroyed.

After the radium treatment there was very slight bleeding except for "one menstrual period." There was considerable discharge and some pain on voiding. It became increasingly difficult for the patient to empty the bladder, and on September 23 retention was complete. An attempt at catheterization was unsuccessful. Examination showed marked improvement of the area treated, the growth around the opening of the urethra and on the right vaginal wall having diminished greatly in size. The bladder was distended, reaching nearly to the umbilicus. The patient's general condition was good and she was sent at once to the hospital where a suprapubic cystostomy was performed. She was in a disturbed mental state for several weeks following the operation. On October 20 she was discharged from the hospital with the suprapubic catheter still in place.

Examination on November 2 showed a marked diminution in the size of the growth and no enlarged glands were palpable. There was no bleeding and the general condition of the patient was good. The tube was still in place, part of the urine being passed by the tube, part by the urethra.

One month later the patient was slightly more comfortable and walking around. The growth had definitely improved. Occasionally there was slight bleeding and discharge. The tube was still worn but no plug required, part of the urine being passed by the urethra.

On Jan. 13, 1929, the catheter was removed as it had not drained for eighteen days. There was more edema of the lower portion of the vulva and slight bleeding and discharge.

During the next five months the patient was able to void normally but the bleeding and discharge increased and the edema of the vulva became more marked. Codeine was given as required for pain.

Examination on June 18 showed the local condition to be about the same, but the inguinal glands were enlarged and the general condition was poor. The patient died on Aug. 15, 1929, one year after treatment.

CASE 2.—A. S., aged seventy-six. The patient was referred to me July 21, 1931, for treatment of a recurrent growth about the urethra. She had had four children and there had been some frequency of urination since the birth of the first child. For the last eighteen months urination had been painful, and there was itching and swelling of the vulva. In November, 1930, the patient had consulted an osteopath who found four lumps around the urethra in which he inserted radium implants. The lumps disappeared but recurred after several months. A second radium treatment had been given early in June, 1931, but the pain and itching increased and no improvement in the growth was noted. She had lost about twenty pounds in the last year.

Examination under the anesthetic showed a slightly relaxed outlet. A growth was found extending from the anterior surface of the urethral orifice almost to the clitoris. There was definite involvement of the urethral orifice, but the clitoris itself was not involved, although there was some edema of the surrounding structures. The growth presented a slightly depressed, ulcerated surface, with fairly smooth

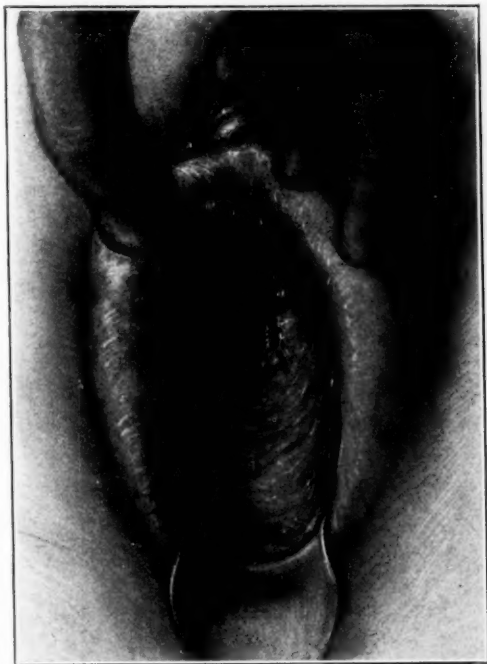


Fig. 3.—Case 2. Carcinoma urethra.

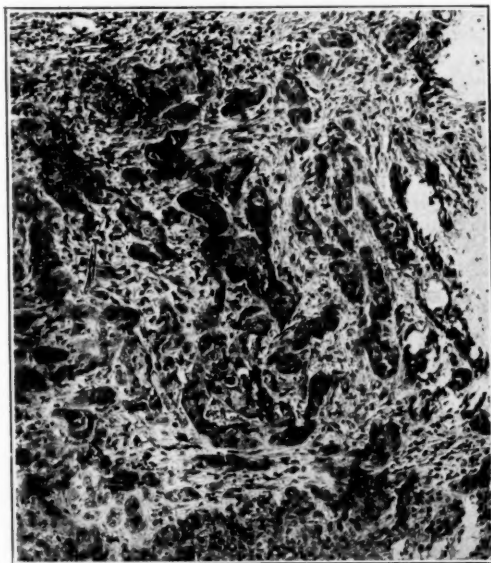


Fig. 4.—Case 2. Squamous cell carcinoma urethra.

edges, the surface of the ulcer being covered by gray membrane, and being about 1.5 cm. in length and 1 cm. in width. Two small portions of the tissue were excised with the knife for microscopic diagnosis which showed squamous cell carcinoma. Ten needles, each containing 1 mg. of radium element screened with 0.5 mm. platinum, and six needles, each containing 2 mg. of radium element similarly screened, were inserted into the growth and into the immediately surrounding edematous tissue so as to radiate the entire palpable growth and the tissue immediately surrounding. Each needle was sutured in position, using braided silk soaked in 1/1000 acriflavine solution. These needles were left in position for one week making a dosage of 3,696 mg. hr. or 28 mc. destroyed. A catheter was kept in the urethra during insertion of the needles. At the finish of the operation this was removed and a retention catheter inserted.

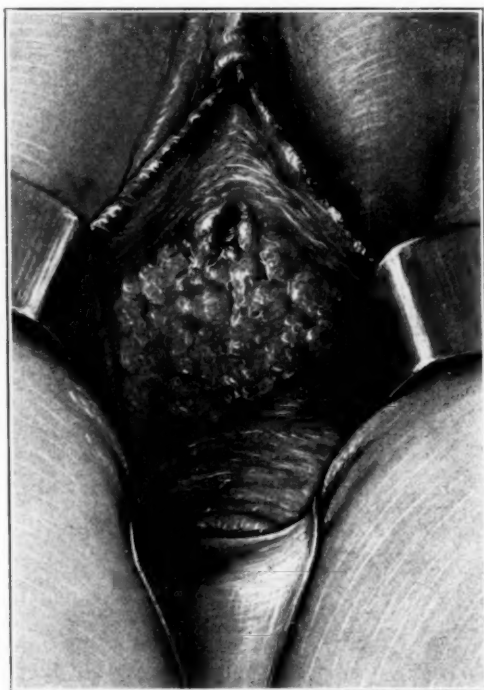


Fig. 5.—Case 3. Carcinoma urethra.

On August 3, when the needles were removed under nitrous oxide anesthesia, there was no change in the appearance of the growth. A traction suture was placed on each side of the urethra for ease in catheterizing the patient, the retention catheter being removed.

On August 15 the patient was examined at home, there being considerable local reaction. Seven weeks later the area of ulceration was about the same size as when originally seen, there was considerable discharge, and membrane formation with edema of the vulva. No extension of the growth could be made out. Codeine was given for pain and a suprapubic cystostomy advised. Two weeks later the patient was more uncomfortable but refused the cystostomy.

There was little change in the growth although the discharge decreased and there was some local healing. The patient died December 23, five months after treatment.

CASE 3.—F. H., aged sixty-four. The patient was first examined Aug. 19, 1932. She was complaining of vaginal bleeding, discharge, and bearing down pain of two

months' duration. She had had four miscarriages and one child, the one birth being normal with no history of lacerations or infection. She had lost about 20 pounds in the last six months.

Pelvic examination was negative except in the region of the external urinary meatus. Here there was a slightly elevated area about 3.5 cm. wide, extending up the anterior wall of the vagina about 3 cm. This appeared to rise from the

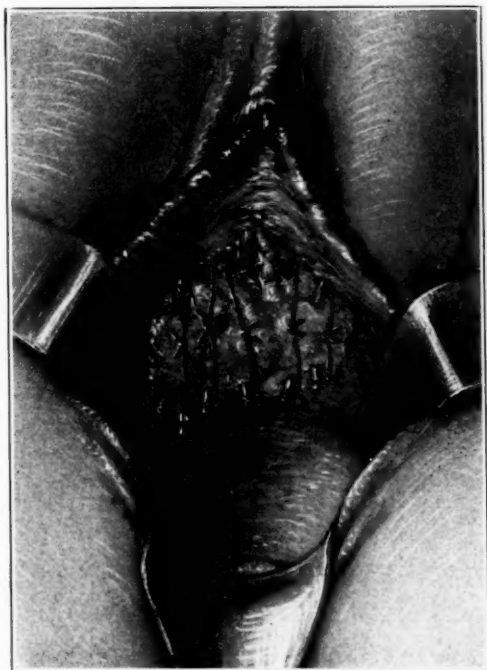


Fig. 6.—Case 3. Carcinoma urethra, with radium needles inserted.



Fig. 7.—Case 3. Squamous cell carcinoma urethra.

posterior portion of the external meatus which was indurated and slightly ulcerated at the edge. The rest of the tumor was nodular, being about 6 mm. thick. It was firmly attached to the wall of the urethra. There was very slight enlargement of the inguinal and femoral glands on both sides. Microscopic examination of tissue removed showed squamous cell carcinoma.

Radium treatment was given on Aug. 30, 1932. A retention catheter was inserted into the bladder with some difficulty on account of the firmness of the urethral wall. Ten needles, each containing 1 mg. of radium element screened with 0.5 mm. platinum, were used. These needles were inserted in the longitudinal direction in pairs, the needles of each pair being tied together with silk that had been soaked in acriflavine solution. One pair of needles was inserted directly in the midline and two pairs in the right and left sides respectively. These needles were left in position for one week, making a dosage of 1680 mg. hr. or 12.72 mc. destroyed. A large rubber tube, doubled upon itself, was placed in the vagina to keep the uninvolved walls away from the radium and the vagina was irrigated with acriflavine solution through this tube.

On September 9, when the needles were removed under anesthesia, the consistency of the growth was found to be much softer, and it had lost its rounded surface and flattened out from an anteroposterior position. The entire growth was covered with a gray-white membrane that ended sharply at the tumor limits. There was a slight purulent exudate.

Examination one month later showed the growth to be about 1 cm. in diameter with a depressed center about 1.5 cm. deep over the urethral orifice. There was no bleeding and no discharge.

On November 9 the patient was examined again and the depressed area over the urethral orifice found to be slightly shallower. The patient said there had been a bloody discharge for one week. She had gained steadily in weight since treatment and her condition is considered satisfactory four months after treatment.

COMPARISON OF METHODS OF TREATMENT

Of the two cases previously reported, one was treated by the surface application of screened radium element and the insertion of steel needles of relatively large radium content for a short time. The second patient, now well nine years and nine months after treatment, was treated by the surface application of screened radium followed after three months by rather limited cautery excision.

In the two most recent cases the patients were treated by the insertion of needles of low radium content, heavily screened, for a long time (one week).

Comparatively simple treatment given promptly is much more effective than more extensive treatment given after the disease has begun to spread.

RECENT CASE REPORTS

Since our last report the following articles dealing with carcinoma of the female urethra have appeared in the literature.

In 1925 Palmer reported one case which was treated by partial resection of the urethra, and in 1926 an article by Schmidt on spindle cell sarcoma of the female urethra appeared. In 1927 Maguire discussed the removal of the bladder and

urethra for malignancy, and Pugh reported one case and Fukai and Yoshida two cases of primary carcinoma of the urethra. In 1928 Fruchard reported one case treated with radium, and in 1929 an article by Nora appeared dealing with epithelioma of the urethra treated by total urethrectomy with restoration of the urethra. Mühsam, Pavlovsky, and Hazelhorst each reported one case in 1930, and in 1931 two articles on this subject appeared, one by Riche and Guibal, the other by Von Mikulicz-Radecki.

I am indebted to Drs. Howard T. Karsner, Marion D. Douglass, and David P. Secof of the school of Medicine of Western Reserve University for the pathologic diagnoses in these cases.

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INTRAPARTUM GAS BACILLUS INFECTION*

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WHEN one considers the maternal mortality from puerperal infection and the rôle that the *Bacillus welchii* may play in its fatal results, one must agree with the closing sentence in Toombs' most recent case report of gas bacillus infection: "The careful reporting of every case observed, and continued experiment as to the best means of prophylaxis treatment, is essential for the control and eradication of this serious hazard to maternity." Wrigley recently consulted the records of the Obstetrical Department of St. Thomas' Hospital and found that in the years 1922-1927 there were 16 deaths from puerperal infection. Of these 16, postmortem examination showed that generalized gas gangrene was present in 6 cases, indeed a remarkable figure when the general impression is that the condition is rare. Comparatively it may be so, but as Toombs has intimated, gas bacillus infection may well be more frequent than one at present realizes.

To date, reports of 56 cases of puerperal infection, due to the *B. aerogenes capsulatus*, appear in the literature. To these, I wish to add another case observed in our clinic.

*Read before the Section on Obstetrics and Gynecology, New York Academy of Medicine, April 25, 1933.

CASE REPORT

The patient, a thirty-five-year-old Jewess with a history of 5 previous pregnancies, was registered in the Woman's Clinic of the New York Hospital on Sept. 15, 1932. The expected date of confinement was Oct. 1, 1932, the Wassermann reaction was negative, and the pelvis was normal in its measurements. She was seen in the antenatal clinic on five successive visits following registration without any abnormal findings.

On Oct. 16, 1932, she was admitted to the delivery floor at 10:45 P.M., after having gone into labor spontaneously at home at 8 o'clock of the same evening. On admission, examination showed temperature 36.2° C., pulse 88 per minute, respirations 20 per minute, and blood pressure 120/75. An average sized child lay in L.O.T., and the fetal heart was 140, L.L.Q. The head was floating, and pains of only fair quality were coming at intervals of four to five minutes. Rectal examination showed: cervix thick and about 1 cm. dilated, membranes intact, and vertex not engaged. The membranes ruptured spontaneously at 3:10 A.M. on October 17. The pains subsided. Beginning at 9:00 A.M. on October 17 she was given a castor oil and quinine induction. This was of no avail. She continued to have only poor pains for the first forty-eight hours, and showed no progress in cervical dilatation; the head remained floating. After 8:00 P.M. on October 18, no one was able to hear the fetal heart again. Suddenly, at 8:00 A.M., October 19, the patient had a chill with her temperature elevated to 39° C. and pulse to 120 per minute. Not long afterward, a vaginal smear and urine specimen were ordered for culture.

About one hour following the chill, the uterus was found rather tense with very little relaxation between the feeble pains occurring every five minutes. There was no external bleeding present. The child's head was still floating and the cervix only 1 to 2 cm. dilated. The patient never seemed to be in shock, but later in the day appeared toxic, as if suffering from an infection. A blood culture was taken. The uterus remained tense. Because of the patient's temperature, the protracted labor, and tense uterus, it was decided to do a sterile vaginal examination in the operating room with immediate preparations for a possible cesarean section. Prior to this vaginal examination, she had had only rectal examinations (12 in number) on the delivery floor and no history of any examinations on the outside.

At 6:45 P.M., under anesthesia, a vaginal examination revealed the following: cervix thick and about 3 cm. dilated; head not engaged, but it was being pushed into the pelvis with a moderately large caput which could be felt through the cervix; a thick, brownish, vaginal discharge with a moderately offensive odor was present. The child's head was dislodged and, as soon as this was done, a large amount of odorless gas escaped from the uterine cavity with a small amount of blood. These findings immediately threw light on the case, and it was felt that we were dealing with an intrapartum infection due to *B. welchii*. A cesarean section, followed by hysterectomy, was promptly performed. As the uterus was incised, a considerable amount of gas escaped. A 3,350 gm., stillborn, macerated, male baby was extracted, the placenta removed, and then a culture obtained from the fundus of the uterus. The uterus was removed supravaginally and both tubes and ovaries were allowed to remain. A cigarette drain was placed in the culdesac and brought through the abdominal wound. The patient stood the operation well and was returned to the isolation pavilion in fairly good condition. Just before the patient was anesthetized, her temperature was 38.4° C. She was given 500 c.c. of 10 per cent glucose intravenously soon after her arrival at the isolation pavilion.

The following morning the vaginal and uterine cultures were reported positive for *B. welchii* and the specimen taken from the uterus was in pure culture. The

patient's condition was satisfactory and her temperature fell to 38.2° C. Her pulse, 120 per minute, was of good quality and the abdomen was soft.

On the second postoperative day she became afebrile and remained so with marked improvement in her condition until the fifth postoperative day. That afternoon her temperature registered 38.4° C. The incision was inspected and it was found that the upper end of it was reddened and slightly edematous. The skin edges at this point were separated and about 15 c.c. of pus with an offensive odor were drained away. The cigarette drain was removed on the third postoperative day. Cultures obtained from the cigarette drain and pus from the incision grew *B. welchii* and *Streptococcus viridans*. Repeated cultures from the incision were taken at frequent intervals during her convalescence. On the eighth day following operation, October 27, the temperature went up to 38.2° C. The following day she complained of pain in the left leg. On November 3, swelling of the left leg was perceptible with added complaint of pain in the left inguinal region. Pelvic and femoral thrombophlebitis had obviously set in as a complication. On November 6, she had a slight cough and complained of pain in the left chest. Chest and throat examination was negative. The pain in the left chest disappeared on November 9 and was explained on the basis of a small pulmonary infarct. She remained febrile up to November 14, the twenty-sixth day following operation. Thereafter she followed an afebrile course. The edema in her left leg gradually subsided and the abdominal incision granulated satisfactorily. On November 28, the fortieth postoperative day, she was allowed to sit up out of bed. Her general condition improved markedly and her convalescence was aided by heliotherapy and a selected diet. Repeated blood cultures were reported negative for *B. welchii* throughout. On November 3, 4, and 7, blood cultures were reported positive for unidentified gram-negative diphtheroids. It was during this time, when these blood cultures were found positive, that the patient complained of pain in the left leg, inguinal region, and left chest. The cultures from the incision were taken and followed until a negative report for *B. welchii* was obtained. This was not realized until December 10, the fifty-second postoperative day. She was discharged in excellent condition on Jan. 19, 1933, ninety-four days after the date of her admission to the hospital.

PATHOLOGIC FINDINGS

Gross.—Gross specimen was a somewhat degenerated placenta. The amnion and the fetal cord showed extensive necrotic changes. The fetal surface of the placenta was anemic in appearance, but was fairly well preserved. Sections were taken through several cavities for microscopic section, and two cotyledons were saved for permanent specimens. Sections were also made through the amnion and through the cord.

The uterus measured 16 by 12 by 8 cm. and the cavity was lined with a necrotic mass of tissue on one side. This was largely a clot of blood, presumably, the placental site. On the other surfaces the tissue was resting in small bullous blebs, so that the surface showed pebbled appearance. Underneath these blebs one hemorrhage of very considerable size appeared. However, under others there appeared to be gas, as there was a crepitation as one pressed upon it with the finger.

Microscopic.—Sections through the musculature of the uterus showed the tissue beneath the placental site to be in every way normal. However the decidua vera had been thrown up into blebs by hemorrhages beneath the decidua, the decidua itself being necrotic, and by the formation of little gaseous cysts. Below the decidua and this area of hemorrhages, the musculature was found to be separated into long cleavage lanes, which separated the muscle bundles from one another, and had gone for a considerable distance, some of them as far as 9 and 10 mm. into the substance of the muscle. This, it was assumed, was due to gas formation also, as in

the preparations of this tissue, which was stained to demonstrate bacilli, the *B. welchii* was found in large quantities along the margins of these gas lanes. An interesting thing in connection with these bacilli was that in many of them one could see two or more spores, the demonstration of spore formation in tissue being somewhat rare and also indicating that perhaps these bacilli showing spore formation were of some age. There was also hemorrhage into these gas lanes at occasional intervals. However, this was not marked. What was very striking was that the tissue in between these cleavage or gas lanes were heavily infiltrated with polymorphonuclear leucocytes. In one or two places one could see that the bacilli were lying inside small lymphatic capillaries and blood vessels.

Placenta.—Some proliferation of the chorionic layers. The notable thing was that the amnion was lifted away from the chorion along its whole margin and that in this space there was marked leucocytic infiltration. The depth of the placenta, however, appeared normal. (a) Section of a cotyledon showed the maternal surface lined completely by adherent decidua basalis. As soon, however, as the fetal surface of the placenta was reached, there was tremendous leucocytic infiltration in all the periphery layer, not more than 1 mm. in depth. (b) Section through amnion was not remarkable, except that it was everywhere outlined with layers of leucocytes, mostly on the fetal surface, but in many places they penetrated to the inner lining. (c) Cross-section of the cord seemed to be singularly free of any leucocytes or other abnormality which could be seen in the hematoxylin eosin stained section. However, on examination of the bacterial stains, the cord was found everywhere to be outlined by masses of bacilli and small streptococci. These have invaded the cord a short distance, and in one of the umbilical veins lying close to the periphery one could see a blood clot, in which there were masses of bacilli, but only an occasional streptococcus.

Bacterial stains of the placenta and those of the amnion showed a distribution of bacilli not on the periphery, as in the case of the cord, but rather in the depth of the tissue, particularly in the subamnion mesothelium.

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BIOPSY SPECIMENS OF THE ENDOMETRIUM

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THE recent advances in our understanding of the physiology of the uterus and its response to various endocrine factors have served to direct attention to the importance of the histologic changes which occur in the endometrium. It has therefore seemed desirable to obtain specimens of the endometrium at frequent intervals as a means of study-

ing various functional disturbances which are characterized mainly by uterine bleeding or periods of amenorrhea. Although various methods have been suggested (Geist,¹ Martin and Ellis,² Klingler and Burch,³), the present study was undertaken in order to determine if the use of "office curettage" as recommended by Kelly could be applied to this purpose.

The curette used in this study was specially constructed with a thin shank so that it could be readily bent. The tip measured 3 mm. in width and 2 mm. in depth. In obtaining the specimen, the patient was placed in the lithotomy position, and the cervix was exposed with a bivalve speculum and carefully cleaned with gauze sponges. Following this, the cervix and os were painted with a 5 per cent alcoholic picric acid solution. The smallest Hegar dilator, No. 1, was then passed into the uterine cavity. This was followed by the next two sizes, Nos. 2 and 3, the cervix then being dilated enough to admit the curette without further discomfort to the patient. The curette was passed through the os until the tip reached the fundus, when it was withdrawn along the anterior surface of the uterus from the fundus to the internal os. The instrument was again introduced and biopsies from the posterior and lateral surfaces of the uterus obtained.

The patients usually complained of discomfort while the cervix was being dilated, but in no instance was an anesthetic or an analgesic necessary. There was very little bleeding immediately following the curettage and only a slight spotting for from one to three days. Several patients were curetted at weekly intervals with no bad effects.

The tissue obtained was immediately fixed in 10 per cent formalin. It was mounted in paraffin and the sections were stained with hematoxylin eosin and with mucicarmine.

Sixty specimens from 53 patients have been obtained to date. The clinical diagnoses were as follows: Amenorrhea 24 cases, metrorrhagia 12, menorrhagia 8, menorrhagia and metrorrhagia 6, menopause 1, sterility 1, and pelvic inflammatory disease 1.

The pathologic studies of these cases will be reported later. Of the 60 biopsy specimens, it was possible to make a diagnosis in 55 instances. In 5 cases an insufficient amount of tissue was secured, but it was possible to repeat the operation successfully in 2 of these.

In patients who have had a short period of amenorrhea, the practice now is to do a Friedman's test before taking the biopsy, in order to definitely eliminate the possibility of gestation. One patient was curetted by error when she was two months pregnant, but no interference with the gestation resulted.

This method is not advanced for the diagnosis of carcinoma, as small lesions may be missed although it seems probable that a very early intrauterine malignancy may occasionally be discovered before it is evident clinically. However, it is still felt that the procedure of choice in patients with suspected carcinoma of the uterus is a thorough curettage under anesthesia.

CONCLUSION

The employment of office curettage to obtain biopsy specimens of the endometrium is a useful and safe procedure in the study of patients with functional pelvic disorders.*

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A CASE OF SPONDYLOLISTHESIS†

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SPONDYLOLISTHESIS, though usually regarded as an orthopedic condition, receives some attention in practically all textbooks on obstetrics. It is striking that, according to Meyerding, obstetricians reported 119 of the 125 cases described previous to 1900. Since the advent of use of the roentgen ray in medical diagnosis, this condition has been found more frequently in men than in women. The same author, reporting 121 cases from the Mayo Clinic, found 85 in men and 36 in women.

The orthopedists consider the fifth lumbar vertebra and the lumbosacral joint a very important section of the spinal column and of special interest in the evolution of man. Meyerding lists the following anomalies that may occur at this site: spina bifida occulta, separation of the neural arch, sacralization of the transverse process and a low-lying fifth lumbar vertebra.

In spondylolisthesis the fifth lumbar vertebra is usually dislocated forward on the sacrum; occasionally the fourth may be dislocated on the fifth and even the third on the fourth lumbar vertebra.

Mrs. M. M., aged thirty-three, para i, native born, came to me for her first pregnancy, July, 1928. First day of last menstruation April 23, 1928. Expected date of delivery Jan. 30, 1929. General physical examination was negative. Height, 142 cm. (4 feet, 8¼ inches).

The pregnancy was uneventful. There was a total gain in weight of 9.7 kilos (21½ pounds) while under observation.

As the pelvis was of the funnel type, the question of cesarean section was discussed but, as the fetal head settled into the true pelvis, it was deemed advisable to permit labor. On Feb. 23, 1929, delivery of a 3,352 gm. (7½ pounds) female child was accomplished by midforceps. Difficulty was experienced at the outlet, and a left lateral episiotomy was done. The puerperium was normal from an obstetric standpoint.

Following delivery, the patient moved to Washington, D. C., and, while there, developed the first of her spinal symptoms. An orthopedic surgeon in Washington was consulted at this time. In April, 1930, she again became pregnant and consulted me in May of that year. After consultation with her New York orthopedist and a letter from the Washington surgeon, both of whom insisted that her preg-

*Since the above report was submitted, 41 additional biopsies have been made without mishap.

†Read before the Section of Obstetrics and Gynecology, New York Academy of Medicine, April 25, 1933.

nancy be interrupted, a therapeutic abortion was done on June 11, 1930. As the outlet was somewhat relaxed, a small perineorrhaphy was done at this time. I did not see the roentgenograms but understood the diagnosis to be arthritis of the spine.

The patient was not seen again until Feb. 17, 1933, when she came in because of another pregnancy. The last menstrual period was about Christmas, 1932. During this interval she had received no treatment for the spinal disease. As another therapeutic abortion was requested, she was referred to Doctor Arthur Krida for consultation. He has epitomized the orthopedic history as follows:

"Her only child is four years of age. Delivery was difficult and, on getting out of bed, she had pain in the back and rectum and a good deal of disability.

"Eight months after delivery, while carrying the baby upstairs the patient felt a sudden giving way in her back. On looking into a mirror, she found her left shoulder elevated and her right hip prominent. The condition became very painful and she was considerably disabled. At the end of ten days she consulted an orthopedic surgeon who applied a plaster of Paris cast in suspension. This

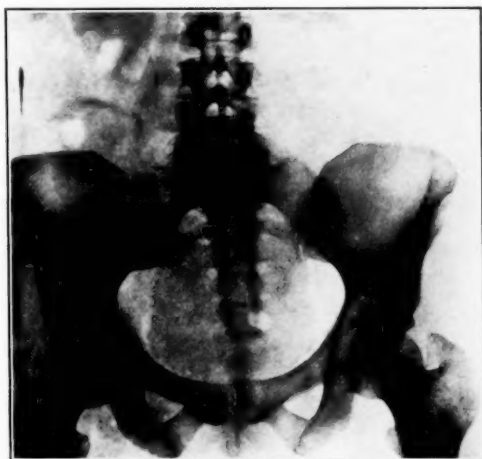


Fig. 1.—Anteroposterior view showing spina bifida of the 5th lumbar vertebra; also 6-piece sacrum and true funnel pelvis.

relieved the pain after a time and she wore the plaster jacket six months, and for the next six months was treated by exercise.

"Since that time the patient has complained of chronic pain in her back, sometimes in both thighs, of weakness, of stiffness of the back, inability to bend and of pain on turning over in bed. The impression received, from her story, is that the back disability has been the source of great distress.

"Examination shows that she is in good general condition. She is short and stocky. There is no deformity. There is some limitation of movement in the lower lumbar spine and on rising from a flexed position, she helps herself up with her hands on her thighs. There is rather marked tenderness on pressure over the fifth lumbar spinous process and to a lesser extent over the left sacroiliac joint. I insisted that Mrs. M. have some x-rays made and these, to my mind, absolutely settle the question as to whether or not she should be allowed to have another baby. Under the conditions, I most emphatically think she should not become pregnant again, because the x-ray shows a rather advanced degree of dislocation of the spine forward on the sacrum. The body of the fifth lumbar vertebra is dislocated anteriorly over half its diameter."

The roentgenologic report by Doctor Klein follows:

"Roentgen examination of the lumbar spine and pelvis shows a marked posterior luxation of the sacrum on the fifth lumbar body and is impinged against the spinous process of this body. There are extensive secondary bone changes of both the destructive and productive type, the latter being more marked.

"Incidentally there is a spina bifida of the fifth spinous process.

"The kidneys are normal in size, shape, and position. There is an irregular radio opaque area on the left side in the region between the second and third transverse processes suggestive of a calcified lymph gland. The sacroiliac synchondrosis and pelvis appear normal."

On Feb. 22, 1933, another therapeutic abortion was performed at the Women's Clinic, New York Hospital. Convalescence was uneventful. The pathologist reported a hydatidiform mole.

175 EAST SEVENTY-NINTH STREET

CARCINOMA OF CERVIX UTERI WITH COMPLETE PROCIDENTIA

WILLIAM F. BOUKALIK, M.D., CLEVELAND, OHIO

(From the Tumor Clinic, Cleveland City Hospital)

A RECENT report stressing the rarity of carcinoma of the cervix with procidentia prompts this report.

Guthrie and Bache, in reporting their case, investigated the literature thoroughly, and found only a small number of cases reported.

Mrs. B. D., aged thirty-three years, widow, American, entered Huron Road Hospital with a chief complaint of prolapse of the uterus with vaginal bleeding.

For seven to eight months before admission to the hospital, there had been metrorrhagia accompanied with a heavy feeling in the pelvis. Prolapse of the uterus had not been noted until a few months previously.

Personal history was negative for any severe illness or operation. She had had two pregnancies, one living child and one miscarriage. There was no history of laceration or infection at the time of the one delivery. The date of these pregnancies was not ascertained. Family history was negative.

Pelvic examination showed a slightly relaxed vaginal outlet. The cervix was enlarged, measuring about 4 cm. in diameter and about 5 cm. in length, lying in the vaginal axis. The surface of the cervix was everywhere smooth except immediately around the opening of the cervical canal. The uterine body was not enlarged and was just anterior to midposition and freely movable. The lateral structures could not be made out definitely. Very slight traction was required to deliver the entire cervix outside the vagina.

Biopsy performed at this time showed squamous cell carcinoma of cervix.

Radium treatment April 21, 1921. Four steel needles with a wall thickness of 0.35 mm., each containing 12.5 mg. radium element, were inserted directly into the cervix, and one tube, containing 50 mg. of radium element screened with 0.5 mm. of silver, 1 mm. of brass, and 1.5 mm. rubber, was placed within the cervical canal. The vagina was tightly packed with gauze. All radium was allowed to remain nineteen hours, making a dosage of 1,900 mg. hours. At the end of this time the

slight traction necessary to remove the needles from the cervix caused the entire cervix to protrude from the vagina. There was no attempt at correcting the prolapse.

The patient was discharged from the hospital the second day after treatment. Convalescence at home was rather stormy, with evidence of pelvic infection which confined the patient to bed for about five weeks. This infection cleared up, bleeding stopped and the cervix decreased in size.

In October, 1925, her physician reported the patient well and symptom-free, although there had been no recent examination.

In September, 1930, the patient was reported in good health and symptom-free, both from the standpoint of bleeding and the prolapse, but did not return for examination.

In October, 1932, the same report was made, this being eleven and a half years after the original treatment.

COMMENT

This is the only case of carcinoma of the cervix uteri and complete procidentia seen by Dr. L. A. Pomeroy in a series of 350 microscopically demonstrated cases of carcinoma of the cervix.

The rarity of these two conditions occurring together has been noted by others and speculation as to why they are so infrequently found together has resulted in varied reasons being advocated. The following explanations summarize the views of several investigators:

1. Carcinoma occurs usually before that time of life when pelvic relaxation permits the development of procidentia.
2. Carcinoma, by fixation of the uterus, prevents relaxation and subsequent procidentia.
3. The free drainage and the lessened vaginal secretion that is present with procidentia diminish the chronic irritation that predisposes to carcinoma.
4. The cornification of the cervical epithelium that is present in procidentia is believed by some to offer a barrier to the development of carcinoma.

At present the above reasons are the most plausible in attempting to explain the rarity of carcinoma of the cervix uteri occurring with complete procidentia.

I wish to express my thanks to Dr. Lawrence A. Pomeroy for the privilege of reporting this case treated by him.

REFERENCE

Guthrie, Donald, and Bache, William: Ann. Surg. 96: 798, 1932.

5644 BROADWAY

DYSTOCIA FOLLOWING CERVICAL AMPUTATION

H. CLOSE HESSELDTINE, M.S., M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology, The University of Chicago, and the Chicago Lying-In Hospital)

SUBSEQUENT to cervical operations, especially high amputations, one of three obstetric complications may develop: (1) Sterility, (2) abortions or premature terminations of pregnancy, or (3) serious dystocia at term, with the associated danger of extensive tears and rupture of the uterus. Since the incidence of these complications influences the indications and types of surgical operations for cervical

diseases during the childbearing period, and one of the potential dangers is illustrated here, the following case is reported.

Mrs. H. R. (No. 53634), aged twenty-three, Irish-Canadian, registered at the Chicago Lying-In Hospital on Jan. 21, 1932, during the fifth lunar month of her third pregnancy, because she was advised that a cesarean section might be necessary.

The antecedent history relates that the two previous pregnancies (1927 and 1928) were uneventful, except for relaxation of the pelvic structures. In June, 1929, a cystocele, rectocele, and prolapse of the uterus was treated by "advancement of the bladder, guillotine amputation of the cervix, shortening of the posterior ligaments, and a perineal repair." No menstrual difficulties developed but some relaxation recurred. The remainder of her past history was irrelevant. Her only complaint was the pregnancy, dating from November 14, 1931. No unusual findings were elicited on general physical, blood or urine examinations. Although the bony pelvis was normal, there existed a moderate rectocele and general redundancy of the vaginal wall. The cervix was lost in the vault of the vagina, where no os could be made out among the numerous folds. The corpus was the size of a twenty-two weeks' pregnancy and contained a fetus developed for that period. The antenatal course was normal.

Labor began spontaneously on June 4, 1932, eleven days after the estimated date of confinement. It was thought that the stump of the cervix was dilating normally. The bag of waters broke at the twelfth hour of labor. However, at the eighteenth hour it became evident that the labor was abnormal. On vaginal examination there was no dilatation of the cervix, but it was completely effaced and the lower uterine segment was found to be very thin. Even though amniotic fluid had been escaping, the examining finger could not be forced into the canal. The occiput (O.L.T.) was at the level of the spines. The delivery of a female fetus, weighing 3,055 gm., was effected by laparotrachelotomy under local anesthesia. The findings at operation confirmed the impression that uterine rupture was imminent. The anterior passive portion of the uterus was so thin that it ruptured when grasped by Allis forceps. The lower uterine segment had expanded posteriorly to fill the whole posterior portion of the pelvis. Since sterilization seemed desirable and the patient's condition was unfavorable for hysterectomy, the tubes were ligated. The short stenosed cervix was dilated to allow the shuttle and the end of the pack to be passed into the vagina.

Except for a slight febrile course during the first thirty-six hours, the convalescence was entirely satisfactory. The patient has had repeated examinations since her discharge from the hospital. The last examination on Jan. 3, 1933, revealed a rectocele and general redundancy of the vaginal walls and a remnant of the cervix at the apex of the vagina, whose canal admitted a fine probe. The uterus was normal in size, shape, position, mobility, contour, and consistency. The adnexa were normal.

Although the complications of hematometria and pyometria were feared, neither one has appeared. Moreover, the patient denies discomfort or incapacity during her menstrual period, and does not wish a vaginal-perineal plastic repair.

5840 DREXEL AVENUE

AN UMBILICAL CORD CLAMP

HOWARD F. KANE, M.D., WASHINGTON, D.C.

(From the Department of Obstetrics and Gynecology, George Washington University)

IN 1922, Willson recommended closure of the umbilical cord by means of a clamp placed immediately adjacent to the skin. Advantages of this method were said to be: "(1) The technic is simple and readily employed by anyone. (2) The cord is practically entirely removed, leaving a minimum of devitalized tissue to drain toxins into the infant's circulation. (3) Drainage from the amount of cord tissue remaining is facilitated. (4) Rapid dehydration is assured, thus preventing infection and insuring early separation. (5) The after-care of babies thus treated is greatly facilitated.

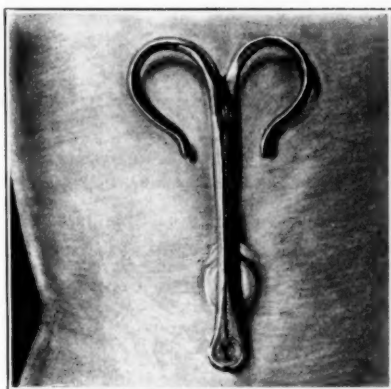


Fig. 1.

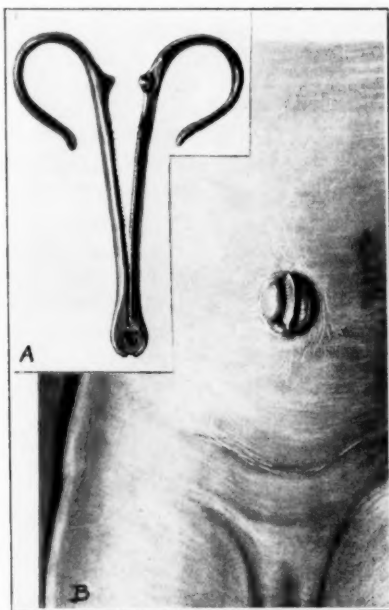


Fig. 2.

Fig. 1.—The clamp in position after the cord clamp has been cut.

Fig. 2.—A, The clamp unlocked. B, The ribbon of tissue which results from compression of the cord.

Since Willson's paper was published, I have employed this method in over 2,200 private patients and several thousand patients have been so treated in wards under my supervision. No deaths have occurred nor has there been a case of infected stump.

A wide variety of clamps has been used, ranging from Kocher forceps to small hemostats, straight, curved and angulated. Several types of clamps devised especially for this purpose have been tried. Each instrument has shown some fault of weight, size, difficulty of application or tendency to slip.

The instrument here presented has been devised in an attempt to eliminate all of the objectionable features found in other clamps. In length it is $3\frac{1}{8}$ inches, it

weighs half an ounce. The jaws are flexible in order that they may maintain a firm hold on the cord as it becomes thinned by pressure, and are slightly curved to conform to the convexity of the baby's abdomen. The closed end of the clamp consists of a hinge rather than of the spring used in a similar model, as it was found that the latter would sometimes fail to compress the cord as firmly as is necessary. Two longitudinal grooves on the inner surfaces of the jaws prevent lateral slipping, and transverse serrations overcome the tendency of the cord to slide out of the clamp during its application. The lock has one catch only, as it was found that the clamp would frequently be closed only to the first notch when applied to the thick cord, and would not hold the thin ribbon of tissue which results from compression. The present model is either locked securely or not at all. The open ends of the jaws are continued into shepherd's crooks, rather than rings, to facilitate the tying of the lock with cord tape by those who feel that this procedure lessens the likelihood of the slipping of the catch. This supposed precaution is of no value as it has been demonstrated that it is possible to unlock the clamp even though it has been tied with all possible firmness.

The cord is clamped as closely as possible to the edge of the skin, and the distal portion is cut flush with the clamp. From six to twelve hours after delivery the instrument is removed, leaving a thin ribbon of completely dehydrated tissue the width of the jaws of the clamp. This paper-thin ribbon and a small flat scab at its base constitute all that remains of the cord. A flat sponge held in place by a bandage is sufficient dressing, and is changed only when it becomes loosened or soiled. In four or five days the vestiges of the stump are usually found loose under the dressing and the navel is entirely healed.

Willson removed the clamp at the end of an hour in order to allow drainage from the stump. Theoretically, compression for one hour is sufficient to insure hemostasis. Trauma and exposure to the relatively cool air cause the muscles of the umbilical arteries to contract, while the vein has been emptied by the negative pressure of the newly established pulmonary circulation. On several occasions, however, hemorrhage occurred after this early removal of the clamp. It has seemed that the loss of a small amount of seepage from the stump is more than compensated for by the additional precaution against hemorrhage.

This instrument seems to provide an ideal means of treating the umbilical cord by a method which has been thoroughly tested and found to be entirely satisfactory.

1835 EYE STREET, N. W.

REFERENCE

Willson, P.: AM. J. OBST. & GYNEC. 3: 506, 1922.

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D., ASSOCIATE EDITOR

Selected Abstracts

Complications of Labor

Schiller, W.: **Prolapse of the Umbilical Cord**, *Monatschr. f. Geburtsh. u. Gynäk.* 88: 52, 1931.

Among 67,859 labor cases there were 587 instances of prolapse of the cord. The most important causative factor was contracted pelvis. In cases where the pelvis was normal a large proportion of the babies were premature. The author emphasizes that absence of pulsation in the cord does not necessarily mean that the child is dead. Breech presentations most readily result in prolapse of the cord; the complication occurred in 50 per cent of the foot presentations and in still higher frequency in transverse presentations, especially in multiparas.

In the present series 8 women with contracted pelvis had prolapse of the cord in more than one labor.

In the treatment of this condition, reposition plays a very minor rôle because other complications are present and these must be overcome or the cord will prolapse again after replacement. The treatment consists in terminating labor as rapidly as possible but this holds only for the cases in which the cervix is completely or almost completely dilated. An attempt should be made to replace the cord unless too much of it has prolapsed, but time should not be wasted in the effort. In the presence of an incompletely dilated cervix the results are much worse for both mother and child. The only certain method of delivery, especially for primiparas, is cesarean section for it gives excellent results.

J. P. GREENHILL.

Andérodias, Mahon and Dagorn: **Prolapse of the Cord**, *Bull. Soc. d'obst. et de gynec.* 6: 537, 1933.

At the Bordeaux obstetric clinic among 11,000 labor cases there were 62 cases of prolapse of the cord (0.56 per cent). Only 20 of the patients were primiparas. The fetal presentations were as follows: cephalic 60 per cent, breech 24 per cent, shoulder 8 per cent, and face 3 per cent. Hence the incidence of abnormal presentations was 35 per cent instead of the usual 3 or 4 per cent. Other complications were polyhydramnion in 18 per cent, contracted pelvis in 15 per cent, very small fetus in 12 per cent, multiple pregnancy in 5 per cent and tumors in the pelvis in 1.5 per cent. In 60 per cent of the cases, the bag of waters had ruptured spontaneously and in 40 per cent, this had been done artificially. The treatment in every case but one was obstetrical and in the one case a cesarean section was performed thereby delivering a live child. In the 61 cases treated conservatively only 31 infants survived, yielding a death rate of almost 50 per cent. Only 16 infants perished because intervention was resorted to too late. Not a single mother died. The authors advise delivery through the vagina in all cases where it is possible to secure both maternal and fetal security by this procedure. Otherwise a cesarean section should be performed without any hesitation.

J. P. GREENHILL.

Bjornson, O.: Posterior Position of the Occiput in Labor, Brit. M. J. 1: 311, 1933.

The author discusses the anatomy and usual methods of diagnosis of occipito-posterior position. The popular methods of treatment are: Manual rotation of the occiput, combined with pressure on the anterior shoulder in the direction of the midline of the abdomen. The method taught by Hodge many years ago was to correct the position by increasing flexion, in which method two fingers are placed in the vagina, making pressure on the bregma. Instrumental rotation is very briefly discussed and declared impractical in the hands of the general practitioner.

The author's method consists of turning the back forward by internal manipulation alone. Under surgical anesthesia, with complete or near complete dilatation and ruptured membranes, the hand is carried above the head and the shoulder is grasped with four fingers over the scapula and with the thumb over the clavicle. After the back becomes anterior the head may be pressed into the inlet and maintained by a tight binder. The author advocates immediate instrumental delivery after the rotation has been completed.

FRED L. ADAIR AND L. E. ARNOLD

Nölting: Frontum Presentations in the Maternity Hospital of Rividavia and in the Maternity Institute, Semana méd. 16: 1236, 1932.

Nölting designates any deflexion attitude at the superior strait a frontum presentation. This condition occurred 37 times in 21,639 cases: Spontaneous delivery 12, forceps delivery 7, internal version 6, cesarean section 5, Thorn's maneuver 2, artificial change to face presentation 2, Schatz's maneuver 1, spontaneous flexion 1, destructive operation 1; maternal mortality 2.7 per cent, fetal mortality 8.1 per cent (internal version 1 death, forceps 2 deaths).

Contracted pelvis was the cause of the dystocia in 48.6 per cent of the cases.

The author believes that in a normal pelvis version is the proper treatment. For a contracted pelvis he advises cesarean section.

JAMES M. PIERCE.

Westman, A.: The Breech Presentations at the Stockholm University Woman's Clinic From 1916 to 1930, Acta obst. et gynec. Scandinav. 11: 112, 1931.

There were 993 breech deliveries representing an incidence of 2.3 per cent. Among the etiologic factors, contracted pelvis, abnormality of the uterus, and polyhydramnios were absent. This presentation was more frequent among primiparas than among multiparas. In 24.6 per cent of the cases the delivery was premature and in 32.8 per cent the bag of waters ruptured before or at the onset of labor. Labor was prolonged in most cases. The maternal death rate was 0.27 per cent. The corrected fetal mortality was 8.8 per cent for all the cases, 11.2 per cent for the primiparas, and 5.2 per cent for the multiparas. Most of the deaths occurred in women over thirty years of age.

The treatment in most cases was expectant. In those delivered spontaneously the fetal mortality was 4.2 per cent for the primiparas and 2.9 per cent for the multiparas. Where manual aid was rendered the figures were 14.5 per cent and 8.3 per cent respectively, and for the operative deliveries the rates were 33.3 per cent and 16.7 per cent.

In cases of early rupture of the membranes and weak pains, the author advocates the use of a bag and the injection of thymophysin. Since the fetal mortality is high in old primiparas, cesarean section should be considered.

J. P. GREENHILL.

Currie, David W.: Injection of the Umbilical Vein in Retained Placenta, Lancet 1: 1087, 1932.

The author in attempting to develop a procedure for forcing the delivery of the placenta without manual removal has used a modified Mojon-Gabaston method. Indications for shortening the third stage are (1) to avoid further blood loss and (2) to avoid the breaking down of the repaired vaginal and perineal lacerations, with the delivery of the placenta. The technic consists briefly of antiseptic preparation of the genitals and cord near the vulva, and the injection into the umbilical vein of from 300 to 400 c.c. of saline in two and one-half minutes. This procedure avoids the danger of introducing infection, shock, rupture of the uterus, and hemorrhage. Such a management is intended only for the unseparated placenta and not for the abnormally adherent one. The placenta is generally delivered within five minutes after this injection, presumably due to the increased size of the placenta within the uterus stimulating stronger contractions.

Methods such as simple expression and even "Credé" may be tried before using the umbilical vein injection.

The author reports his series of 13 cases, with only one failure, which may have been the result of too slow an injection.

This method is applicable for the general practitioner.

H. CLOSE HESSELTINE.

Clason, Sam: Results of Manual Compression of the Aorta in Hemorrhage of the Third Stage of Labor, Acta. obst. et gynec. Scandinav. 13: 127, 1933.

As the result of 529 cases in which manual compression of the aorta was used to arrest pathologic hemorrhages during the third stage of labor, the author points out that the procedure can be used to advantage in any kind of hemorrhage, whether due to lacerations or to atony of the uterus; and, in the latter case, whether the placenta has been expelled completely or not. He also shows that manual compression of the aorta before the placenta is expelled does not in the slightest degree interfere with, but rather assists the expulsion. He further demonstrates that when it is used in cases of atonic hemorrhage, following complete expulsion of the placenta, satisfactory hemostasis may be counted on in over 95 per cent of cases.

J. P. GREENHILL.

v. Probstner, A.: Five Cases of Uterine Rupture Following Incorrect Use of Hypophyseal Preparations, Med. Klin. 26: 1785, 1930.

Five cases of rupture of the uterus are reported by v. Probstner. These cases were observed during the last four years and all were due to the injudicious use of pituitary preparations. Four of the mothers died in spite of operation. The only mother who was saved had an incomplete rupture, and the treatment in this case was tamponade. The author maintains that the pituitary preparations were not at fault but the incorrect use of them. He says that small doses of these preparations, namely 0.5 c.c., should be used at first, and then this dose or a larger one may be repeated. He condemns the use of hypophyseal preparations simply for the purpose of shortening labor in a case where labor is progressing normally. Neither should they be used routinely in the third stage of labor. Among the contraindications he mentions heart and kidney disease, eclampsia, and cephalopelvic disproportion. After the administration of these preparations, the physician should remain with the patient until the effects of the drug have all worn off.

J. P. GREENHILL.

Sachs, Heinz: Rupture of the Uterus During Labor, *Zentralbl. f. Gynäk.* 54: 1180, 1930.

In a series of 20,800 deliveries at the Koenigsberg Clinic during the years 1910 to 1929, there were 36, or 0.2 per cent, complicated by rupture of the uterus. Curiously enough, not a single case occurred in an old cesarean section scar. Spontaneous rupture was observed more frequently in multiparas than in primiparas, while violent rupture was more frequent in women bearing their first, second, or third child.

Symptoms of impending rupture were, subjectively, marked malaise; objectively, definite retraction ring (14 per cent of the cases). Of the 15 spontaneous ruptures 10 were complete, and of the 15 women, 40 per cent were saved by hysterectomy. The total mortality in this group of complete ruptures was 53 per cent, 33 per cent of whom died of infection. Of 21 cases of violent rupture following injury to the uterus, 6 were complete, 3 were incomplete, and 12 were cervical tears. Half of these cases were treated by hysterectomy. The total maternal mortality was as follows: complete ruptures, 66 per cent; incomplete ruptures, 31 per cent; cervical tears, 23 per cent. Fetal mortality in the entire series was 80 per cent.

WILLIAM F. MENGERT.

Grimault, L.: Rupture of the Uterus During Labor After Injection of Pituitary Extract, *Bull. Soc. d'obst. et de gynéc.* 4: 292, 1932.

Grimault reports the case of a thirty-year-old para vi who was given a hypodermic injection of pituitary extract because of slow labor. This was followed by violent uterine contractions, which, after a time ceased entirely. Hemorrhage occurred and the fetal heart could no longer be heard. The child was delivered by version and extraction after which a rupture of the uterus was discovered. A hysterectomy was performed and the patient recovered.

J. P. GREENHILL.

Bey, N. Mahfouz: Rupture of the Uterus, *J. Obst. & Gynec. Brit. Emp.* 39: 743, 1932.

One hundred and ten patients with ruptured uterus are included in this report, covering a period of twenty-eight years. The etiologic factors are classified as follows: Contracted pelvis 52, neglected shoulder presentation 26, hydrocephalus 4, pathologic anteversion due to pendulous abdomen 8, persistent occipitoposterior 6, breech 4, complex presentation 3, posterior asynclitism in a borderline pelvis 1, ruptured cesarean scar 1, twins 1, bicornute uterus 2, pathologic anteversion due to ventral fixation 2.

Two tears were fundal, and of these one was the scar of the only previous cesarean section in the series. Thirty-seven per cent of the tears were on the left lateral border of the uterus, and 22 per cent on the right. Two-thirds of all the cases were traumatic in origin, with delivery through an imperfectly dilated os. The remaining one-third occurred spontaneously. The vaginal vault was involved in 13 per cent of the cases. There was no case of rupture of an uterine scar resulting from antecedent myomectomy, though the author has delivered 10 such patients.

The author advises that each case be estimated from the standpoint of shock and sepsis before undertaking laparotomy, and says that, "expectant treatment, with all its defects, remains the safest method of treatment in the circumstances." Laparotomy, however, "is the treatment of choice under the following conditions: (1) When hemorrhage cannot be controlled by the expectant method. (2) When the placenta or fetus has escaped into the peritoneal cavity. (3) In cases in which hemorrhage recurs after plugging. (4) When delivery of the fetus by the vagina is difficult or not advisable."

The mortality of patients treated by laparotomy was 55 per cent, while that of patients treated expectantly was 62.9 per cent. However, if this latter figure is corrected by subtracting those patients who were admitted moribund, and those who died before any treatment could be instituted, it becomes 56 per cent.

WILLIAM F. MENGERT.

Bohler, E.: Four Cases of Uterine Rupture, Bull. Soc. d'obst. et de gynéc. 1: 108, 1931.

The author reports four cases of rupture of the uterus. The first occurred spontaneously after a normal labor. The patient was not seen until forty-eight hours after the accident occurred, and she died twelve hours after hysterectomy. The second rupture occurred during version and extraction for a transverse presentation. The patient recovered after a hysterectomy. The third rupture took place during the Delmas method of forcibly dilating the cervix for placenta previa. Hysterectomy was performed and the patient recovered. In the fourth case there was an extensive laceration of the cervix and culdesac. This was packed. A large hematoma was found in the broad ligament and this became infected. After drainage was secured, the patient got well.

J. P. GREENHILL.

Tolosa, Benedicto: An Analysis of Thirty-two Cases of Uterine Rupture, Rev. ginec. e d'obst. (Rio de Janeiro) 1: 2, 1933.

Covering a series of 32 cases of rupture of the uterus the author finds as etiologic factors: *Trauma* in 8 cases (version 6; forceps 2). *Spontaneous* in 24 cases (during gestation 2, during labor 22). One of the ruptures during pregnancy occurred in a cesarean scar. Of the cases occurring during labor 16 ruptures were caused by dystocia, 2 by oxytocics, 1 by phlegmonous edema, in 3 instances cause unknown.

As to prognosis: all cases operated, 8 recovered and 24 (75 per cent) died, 12 from hemorrhage and 12 from peritonitis.

In 10 instances the tear runs longitudinally, in 22 transversely.

The writer draws the following conclusions: Uterine rupture is the gravest complication in obstetrics. Hemorrhage and peritonitis are the most common causes of death. Of all obstetric operations version is the one most likely to cause rupture of the uterus. Traumatic ruptures are longitudinal, spontaneous are transverse. The nonrecognition of dystocia and ignorance concerning indications for administration of pituitrin are responsible for 82 per cent of the uterine ruptures.

JAMES M. PIERCE.

Stacey, J. Eric: Failed Forceps, Brit. M. J. 2: 1073, 1931.

A case of "failed forceps" is defined as one wherein an unsuccessful attempt with forceps was followed with delivery later by forceps or some other method. A total of 154 cases are reviewed.

As to etiology of the difficulty, 115 had early rupture of the bag of waters; in 88, or 77 per cent, this had been done artificially before complete dilatation of the cervix. In 100 cases, or 66 per cent, the cervix was not completely dilated when the forceps were attempted. Forty-six cases had contracted pelvis, but in less than half of these did this seem to be the sole factor. There were 48 cases of occiput posterior position, mostly unrecognized. Twenty-four miscellaneous causes were manifest, such as face and transverse presentations, monsters, etc.

Eventual delivery followed spontaneously in 33 cases (25 per cent), usually after waiting for an occiput posterior to rotate, or for the cervix to become completely

dilated. The author thought that this figure would have been much higher save for the premature attempts at forceps delivery. Sixty-four cases (42 per cent) were finally delivered by forceps; in nearly half a manual rotation to the anterior position made the forceps delivery relatively easy. Severe maternal lacerations, poor fetal heart tones, and even palpable fetal skull fractures forbade cesarean section in many cases. In fact, in only nine cases was abdominal delivery thought to be feasible. In 41 cases either craniotomy or embryotomy was necessitated.

The end-results were alarming: 24 mothers died (16 per cent), and less than half of the babies left the hospital alive. Twenty-five per cent of the cases had a morbidity according to the B.M.A. standard and 19 other cases were definitely febrile. More appalling results could hardly be cited from any other series of obstetrical cases. The author followed all but 15 of the surviving cases and found an exceedingly high percentage of permanent morbidity, ill health and sterility.

ARTHUR B. HUNT.

Heyman, J., and Lundqvist, A.: The Symphysis Pubis in Pregnancy and Parturition, Acta obst. et gynec. Scandinav. 12: 223, 1932.

Heyman and Lundqvist have made a roentgenologic study of the symphysis pubis. They describe in detail the technic employed by them for the purpose, and discuss possible sources of error.

The investigation comprises 74 cases of pregnant women, and a series of 8 cases roentgenographed during labor.

Variations in the width of the symphysis invariably consist in an increase of the separation before parturition, followed by a decrease in width after delivery. It is probable that an increase in the width takes place in all women during pregnancy. It is also probable that the widening ceases two or three months before parturition, and there are good reasons for supposing that it commences in the early stages of pregnancy.

The measurable widening is slight. In the roentgenographs it varies from 1 to 12 mm., which corresponds to an actual difference of from 0.5 to 7 mm.

The symphysis does not increase in width during labor. An actual separation of the pelvic bones during labor, a disjunctio pelvica in the sense suggested by Hippocrates, is hardly to be imagined. The authors consider the demonstrated widening of the symphysis as part of an active biologic process, begun in the early stages of pregnancy, and tending, like similar processes in the sacroiliac joints, to increase the roominess of the pelvis.

After delivery, the symphysis appears to reassume its original width. Certain observations seem to indicate that the variations are greater in multiparas than in primiparas.

J. P. GREENHILL.

Reis, Ralph A., Baer, Joseph L., Arens, Robert A., and Stewart, Ellen: Traumatic Separation of the Symphysis Pubis During Spontaneous Labor, Surg. Gynec. Obst. 55: 336, 1932.

The world literature to date has yielded only 62 instances of separation of the symphysis pubis during spontaneous labor, to which are added 5 additional case reports from the maternity service of the Michael Reese Hospital.

Separation of the symphysis pubis is due to marked intensity of the uterine contractions and marked rapidity of labor. Multiparity and relative disproportion are additional etiological factors. The force that causes the separation of the symphysis pubis is a wedge effect produced by the violent thrust of the fetal head through the superior strait.

The bony gap demonstrable by x-ray or by actual palpation is never a criterion of the existence or the degree of the injury.

No characteristic changes in the symphysis pubis due to pregnancy could be determined by x-ray.

Pain in the affected joint is usually the first as well as the predominating symptom of separation of the symphysis pubis. The typical physical findings are diagnostic and include edema and swelling, tenderness, pain on pressure, and a waddling gait which is characteristic of the condition.

The proper treatment consists in absolute bed rest, pelvic immobilization which can be achieved by sandbags, adhesive tape, open operation or circular compression by pulley and weight.

WM. C. HENSKE.

Zarate, E.: Zarate Technic of Partial Symphyseotomy, Arch. f. Gynäk. 147: 749, 1931.

The author describes his technic for partial symphyseotomy and discusses its great value for labor in contracted pelvis. He describes it as the most simple and safe of all obstetric operations. It practically replaces forceps and version but not the Kristellar expression and episiotomy. He cautions against the use of pituitary extract following partial symphyseotomy because of the danger of rupture of the anterior vaginal wall. It is desirable that the patient remain in bed for at least twenty-one days. The operation is contraindicated when the conjugata vera is less than 8 cm., in rigid cervix, in rigidity of vagina, etc.

His statistics for 2,950 patients with contracted pelvis are as follows:

	INCIDENCE	MATERNAL MORTALITY	FETAL MORTALITY
Forceps	3.35%	2.12	36.17
Version-extraction	14.07%	2.56	35.76
Cesarean section	3.95%	7.27	7.27
Spontaneous labors	66.00%	0.53	6.95
Symphyseotomy	3.95%	0.00	0.00

RALPH A. REIS.

Gardner, M. E.: Pubiotomy, Med. Woman's J. 38: 36, 1931.

Pubiotomy as the procedure of choice in the borderline pelvis is advocated. In the young primipara it permanently enlarges the size of the pelvis, offering easy subsequent deliveries, in contrast to obligatory future operations if a cesarean section is elected for the first. In the potentially infected case it is much safer than trachelolaparotomy. The bone injury heals rapidly with a fibrous union and a permanent widening of the pelvic girdle. Normal use of the limbs may be expected at the end of two weeks. An illustrative case is presented.

FRANK SPIELMAN.

Books Received

HANDBUCH DER INNEREN SEKRETION. Herausgegeben von Dr. Max Hirsch in Berlin. II. Band, Lieferung 10. Verlag von Curt Kabitzsch. Leipzig, 1933.

PRACTICAL MEDICAL DICTIONARY. By Thomas Lathrop Stedman, M.D. Twelfth revised edition. Illustrated. William Wood and Company, Baltimore, 1933.

COMBINED TEXTBOOK OF OBSTETRICS AND GYNAECOLOGY, for students and medical practitioners. By J. M. Munro Kerr, Glasgow University; J. Haig Ferguson, Royal Infirmary, Edinburgh; James Young, Royal Maternity, etc., Edinburgh; James Hendry, University of Glasgow, with contributions from Charles McNeil and J. Duncan White. Second edition, revised, rewritten and enlarged, containing 497 illustrations and additional x-ray plates. William Wood & Co., Baltimore, 1933.

MATERNAL MORTALITY AND MORBIDITY. A study of their problems. By J. M. Munro Kerr, Regius Professor of Midwifery, University of Glasgow, etc. Illustrated with maps, diagrams, charts, skiagrams, and hospital plans. William Wood and Co., Baltimore, 1933.

STOFFAUSTAUSCH ZWISCHEN MUTTER UND FRUCHT DURCH DIE PLACENTA. Von H. Schlossmann, Duesseldorf. Mit 8 Abbildungen. Verlag von J. F. Bergmann, Muenchen, 1933.

TEXTBOOK OF PHYSICAL THERAPY. By Heinrich F. Wolf, M.D., Mt. Sinai Hospital, etc. Illustrated. D. Appleton—Century Company, Inc., New York, 1933.

OBSTETRICAL NURSING. By Carolyn Conant van Blarcom, R.N. Third edition, revised. With 251 illustrations and 12 charts. The Macmillan Company, New York, 1933.

Item

American Board of Obstetrics and Gynecology

Written examination for Group B. candidates will be held in various cities of the United States and Canada, April 7: *Oral and General* examination for all candidates in Cleveland, June 12, immediately prior to meeting of the American Medical Association. Reduced railroad rates will be available and all applicants are urged to register in the Section and attend the scientific sessions.

A dinner and round table conference will be held at the Hotel Cleveland, Cleveland, on the first day of the scientific session of the American Medical Association, Wednesday, June 13, at seven o'clock. All Diplomates are requested to be present and physicians interested in obstetrics and gynecology are invited to attend. New Diplomates granted certificates at the examination held immediately preceding the American Medical Association Convention will be introduced individually.

For further information and application blanks for these examinations apply to the Secretary, Dr. Paul Titus, 1015 Highland Building, Pittsburgh (6), Pa.